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THE THERAPEUTIC USE OF ANTITOXIN IN EXPERIMENTAL TETANUS*

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THE widespread prophylactic use of tetanus antitoxin has very effectively reduced the incidence of clinical tetanus. The results during the last World War, furthermore, proved conclusively that tetanus ensuing after the prophylactic administration of antitoxin tends to be mild in character, with a long period of incubation and a lowered mortality.[1] The introduction of active immunization with tetanus toxoid on a large scale undoubtedly will further decrease the occurrence of this disease. Nevertheless, cases still occur and the problem of treatment remains an important and to a large degree an unsolved one.

Recent studies have put the pathogenesis of tetanus on a sound basis and have made the problem of treatment more rational than formerly. Serious doubt has been cast upon the nerve carriage theory which has long dominated the experimental literature and which has so influenced the clinical concept of the disease and of its treatment.[2-6] Tetanus, in our view, is a disease with dual manifestations: (1) stiffness or rigidity of muscles due to the direct action of the toxin upon the peripheral nerve organs in muscle tissue and (2) reflex spasms due to the action of toxin on the motor cells of the central nervous system. Local tetanus is characterized by the local spread of toxin through a muscle or groups

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of contiguous muscles with poisoning of the nerve end organs and consequent stiffness. The rigidity of the musculature in general tetanus is due to the diffuse distribution of the toxin by way of the blood stream to the end organs of many voluntary muscles. The convulsive manifestations of the disease and in most cases death are due to the deposition of blood-borne toxin in the central nervous system.[2-10] Since the toxin is distributed throughout the body and into the central nervous system by the blood-lymph system, it is obvious that the direct blocking of peripheral nerves with antitoxin as advised long ago by von Behring[11] has no rational basis. The demonstration in experimental animals by Abel and his associates[12, 13] that antitoxin has no therapeutic effect, once a lethal amount of toxin has been fixed by the body tissues and the period of incubation has passed, has made it clear why certain patients with tetanus are apparently beyond help. The theory of the alteration of tetanus toxin in the central nervous system into a new lethal agent and the inefficacy of tetanus antitoxin, once a fatal dose of toxin has been fixed in the cord or brain stem and symptoms have developed, likewise point to the futility of treatment in such cases.[8, 10] But, since there is no method by which we can determine whether a given patient with tetanus has or has not already fixed a lethal amount of toxin, we must continue to treat actively all patients in the hope of curing those who are not already doomed and who might otherwise die.

In an effort to understand better the action of tetanus antitoxin, we have been engaged for several years in a series of experiments. Certain of these have been previously described.[10] Others dealing with the protecting value of antitoxin against toxin introduced by various routes will be reported in detail shortly,[14] together with a full discussion of related problems. In the present communication we shall first discuss some of these general problems relating to antitoxin and shall then present fully some studies concerning the best mode of administration of antitoxin as a therapeutic agent.

GENERAL CONSIDERATIONS

Tetanus antitoxin is standardized in this country in terms of the American unit. One American unit of tetanus antitoxin is, by definition, ten times that amount of antitoxin which, when mixed in vitro for one hour with a standard test dose of toxin (equivalent to 100 minimal lethal doses) and then injected subcutaneously, will for four days prevent the death of a 350 Gm. guinea pig.* The standardization of antitoxin is on a sound basis and is especially accurate in this country where a single test toxin is employed.[16-18] But the simple definition of the antitoxic unit tells us little or nothing of the behavior of antitoxin in the animal body. We were especially anxious to know the relative efficacy

*Control studies are done simultaneously with a standard antitoxin of known strength.

of antitoxin in the blood-vascular system of an animal against tetanus toxin in general and specifically against toxin introduced by various routes. We were also desirous of learning whether the efficacy of antitoxin varied in tetanus-sensitive and tetanus-resistant species. We shall summarize the results of these studies.[14*]

The protecting value of antitoxin varies, for some unknown reason, in different species. Antitoxin is less effective in the very tetanus-sensitive guinea pig than in the slightly less sensitive mouse and is still less effective than in the tetanus-resistant dog and cat; and yet the variation is not directly proportional to the sensitivity or resistance of the species. It cannot be accounted for on the basis of the difference in the lethal dose in the various species, nor on the basis of difference in concentration of the antitoxin. This relative inefficiency of antitoxin in protecting against toxin in sensitive animals (man is probably of the same order of sensitivity as the guinea pig and the monkey) is of no real consequence as far as its clinical application is concerned, for the same effect can be easily obtained by giving a sufficiently large amount of antitoxin.

A given amount of antitoxin will protect against from two to eight times more toxin if the two are mixed in vitro before injection than if they are delivered directly into the blood stream. This we interpret as meaning that, given a certain amount of toxin and a slight excess of antitoxin (as measured by the "in vitro protecting value") in the blood of an animal, each molecule of toxin is not completely neutralized *instanter,* thus affording an opportunity for some molecules of toxin to escape into the central nervous system (and other tissues) where fixation and perhaps alteration may occur so rapidly that they cannot become neutralized unless there is a sufficient excess of antitoxin. Abel and his co-workers[12] have demonstrated that some of the toxin which finds its way into the blood stream of animals passes rapidly out of it and becomes fixed in the tissues in an unrecoverable state. They[13] presented evidence to support their suggestion that fixed toxin actually can be neutralized, provided, however, that the antitoxin is available before a certain portion of the incubation period has elapsed and provided that a large excess of antitoxin is present.† In speaking of toxin which is circulating in the blood-lymph system, Abel and Chalian[13] state that it is as completely and easily neutralized by injected antitoxin as would be the case in an in vitro experiment. Although our experiments would indicate that this statement is not quantitatively true, it is absolutely correct in principle, since the toxin requires only a sufficient amount of antitoxin for its speedy and complete neutralization.

*In these studies the antitoxin was given intravenously immediately before the toxin was injected.

†This observation is opposed to the concepts of earlier workers who believed that no fixed toxin could be neutralized by antitoxin.[19-21]

Antitoxin introduced intravenously is less effective against toxin deposited subcutaneously, intramuscularly, or intradermally than it is against toxin injected into the blood stream. Although clinically toxin is generally liberated in the subcutaneous or intramuscular tissues, our observations again give little cause for concern in clinical cases for, although antitoxin is slightly less efficacious against toxin in these tissues than against that circulating in the blood stream, an excess of antitoxin neutralizes the toxin completely and effectively.

With regard to the protecting value of antitoxin injected into a vein against toxin introduced directly into the cord, we found that an entirely different situation exists. If toxin is placed directly into the lumbar cord of dogs, it takes over 8,000 times more antitoxin (injected intravenously immediately before the toxin is injected) to prevent death than if the toxin had been injected into the blood stream, and about 3,500 times more antitoxin than if the toxin had been placed in the muscle. We have previously reported similar experiments.[10] Furthermore, we have shown that far greater amounts are necessary if the administration of antitoxin is delayed for some time after the deposition of toxin in the cord and that, if the interval is prolonged until symptoms have intervened, even enormous doses of antitoxin will not save the animal.

The problem of neutralization of toxin within the cord is simply a matter of bringing to these poisoned tissues soon enough a sufficient quantity of antitoxin.[10] For example, to prevent the appearance of symptoms in the dog after the injection of a fatal quantity of toxin into the medulla, it suffices, if the administration of antitoxin is delayed five hours after giving the toxin, to place into the same area in the medulla 800 times as much antitoxin as could have sufficed to neutralize that toxin had it and the antitoxin been injected simultaneously into the blood stream; whereas, if the antitoxin is injected into the blood stream instead of into the medulla, 800,000 times as much antitoxin is required as would have sufficed had both been placed in the blood stream. It is well known that there is no absolute blood-brain barrier to antitoxin. Such experiments as we have cited, however, show the difficulty of bringing to the poisoned central neurons a sufficient amount of antitoxin quickly enough.

Our studies have led us to the belief that it is the toxin fixed within the central nervous system which is generally responsible for death. Undoubtedly the general metabolic disturbance and the attending loss of weight and strength and the fatigue may be contributing factors, and an occasional patient with tetanus may die without any convulsive manifestations at all, possibly from paralysis of the muscles of respiration. The experimental data indicate, however, that it is the toxin in the central nervous system which is ordinarily responsible for death.

We have suggested[22] that natural resistance to tetanus may depend upon the species ability to prevent the fixation within the central nervous system of an amount of toxin which will cause death.* Certain considerations, furthermore, make it appear plausible that a similar important mode of action may be utilized in acquired active and passive immunity.

Once tetanus toxin is being deposited in the central neurons the great problem is its neutralization before it has become fixed or altered or during the early phase of fixation when it is still neutralizable. In contrast with this very difficult problem we have demonstrated that free toxin in the skin, subcutaneous tissues, muscles, or blood is readily and completely neutralized by the simple administration of a sufficient quantity of antitoxin intravenously.† What is the best manner of bringing as much antitoxin as possible as quickly as possible to the central nervous system?

EXPERIMENTS CONCERNING THE BEST METHOD FOR THE THERAPEUTIC ADMINISTRATION OF TETANUS ANTITOXIN

Experiment 1 (Table I).—Twenty-one hours after the injection of 2 G-P LD50's of tetanus toxin into the thigh muscles of guinea pigs, varying amounts of antitoxin were injected into the cisterna in one group and into a vein in another. In the group in which the animals received antitoxin by intracisternal injection only the single animal which received 1 unit of antitoxin died, and all those which received 2 or more units survived. In contrast to this, only those animals in the group receiving antitoxin intravenously which were given 20 units or more lived. When the administration of antitoxin was delayed until twenty-three hours after injection of the toxin, at a time when the local tetanus was approximately of the same degree as in the preceding part of the experiment, half of those animals which received 1 to 2 units of antitoxin into the cisterna survived and 83 per cent of those which received 10 to 50 units. Of those which were given antitoxin intravenously only the one which received 100 units survived. In a third group treated with similar amounts of antitoxin given intramuscularly none survived. When treatment was instituted twenty-eight hours after

*Wolff-Eisner had previously suggested a similar idea.[23] Roux and Borrel[20] from their experience with "cerebral tetanus" and from studies with diphtheria toxin in rats and morphine in rabbits made the same suggestion. Inadvertently, reference to the latter was omitted in our original communication.

†Our experiments mentioned up to this point deal largely with the protection against toxin afforded by antitoxin given immediately before the injection of toxin and by the intravenous route. Antitoxin given intravenously was found to give better prophylactic protection than antitoxin given by other routes. In guinea pigs and in dogs we have found that antitoxin injected into the cisterna is less efficient than antitoxin given intravenously in protecting against toxin introduced immediately afterwards, either into a vein or into a muscle. Furthermore, although no complete investigation on this point was undertaken, a few observations suggest that antitoxin given subcutaneously or intramuscularly is less effective than that given intravenously. This is as might be expected, for toxin injected by any of these routes is absorbed into the blood stream and should be more quickly and effectively reached by antitoxin injected directly into the blood than by antitoxin placed elsewhere.

TABLE I

THE THERAPEUTIC EFFECT OF TETANUS ANTITOXIN GIVEN BY VARIOUS ROUTES, IN GUINEA PIGS WITH LOCAL TETANUS*

AMOUNT OF TETANUS ANTITOXIN IN AMERICAN UNITS	ROUTE OF ADMINISTRATION OF ANTITOXIN					
	INTRACISTERNAL			INTRAVENOUS		
	NO. OF ANIMALS	NO. SURVIVING	AVERAGE SURVIVAL IN DAYS OF THOSE THAT DIED	NO. OF ANIMALS	NO. SURVIVING	AVERAGE SURVIVAL IN DAYS OF THOSE THAT DIED
T. A. T. given 21 hr. after toxin. All animals had slight local stiffness.						
1	1	0	7	1	0	6
2-7	4	4		4	0	6.5
10-20	2	2		3	1	12
25-154	8	8		7	7	
T. A. T. given 23 hr. after toxin. All animals had slight local stiffness.†						
0.1-0.8	4	0	5	4	0	4.5
1.2-2.0	2	1	8	3	0	5.7
3-7				3	0	6
10-50	6	5	5‡	6	0	8
100	1	1		1	1	
T. A. T. given 28 hr. after toxin. All animals had moderate local rigidity.						
10-50	3	0	7	3	0	3
70-100	2	0	7	2	0	2.5
150-200				2	0	2.5
300-400	2	0	3	2	0	3.5
500	1	0	8	1	0	6
Controls. No tetanus antitoxin.						
0	17	0	3.3			

*Each animal received 2 G-P LD50's of toxin intramuscularly in a single dose in the thigh.

†Of 16 animals likewise treated with varying doses of tetanus antitoxin (0.1 to 100 A.U.) intramuscularly, none survived.

‡This animal kept head turned to left as if the brain stem had been traumatized at the time of injection. Autopsy showed no gross change.

injection of the toxin, none of the animals survived, although those which received antitoxin intracisternally lived longer than those which received it intravenously. This experiment demonstrated amply, we believe, the greater therapeutic efficacy of intracisternally over intravenously administered antitoxin in guinea pigs with local tetanus, all of which without treatment would have developed general tetanus shortly and died within forty-eight hours.

Experiment 2 (Table II).—We next attempted to evaluate this method of treatment in guinea pigs with general tetanus. Forty-eight hours after the intravenous injection of 2 G-P LD50's of toxin all the animals had unmistakable general tetanus. They were treated with varying doses of antitoxin intracisternally and intravenously. None survived, and there was little difference between the two groups. This failure, as well as the failure to save life in the third part of Experiment 1, is undoubtedly due to the fact that in these animals a lethal quantity of tetanus toxin had already been fixed and altered at the time treatment was begun.

TABLE II

THE THERAPEUTIC EFFECT OF TETANUS ANTITOXIN GIVEN INTRACISTERNALLY AND INTRAVENOUSLY IN GUINEA PIGS WITH GENERAL TETANUS*

AMOUNT OF TETANUS ANTITOXIN IN AMERICAN UNITS	ROUTE OF ADMINISTRATION OF ANTITOXIN			
	INTRACISTERNAL		INTRAVENOUS	
	NO. OF ANIMALS	AVERAGE SURVIVAL IN DAYS†	NO. OF ANIMALS	AVERAGE SURVIVAL IN DAYS†
70	2	4		
140	2	4	2	3.7
210-280	4	3.3	4	3.7
350-500	6	4.7	6	3.8
560-700	4	4	6	4.3
Controls. No tetanus antitoxin.				
0	9	2.8†		

*Each animal received 2 G-P LD50's of toxin intravenously. The T.A.T. was given 48 hours later, when all the animals had definite general tetanus (stiffness of body, erection of ears, etc.).

†All the animals died of tetanus.

Our problem then was to arrange an experiment in which we should have animals which were poisoned with more than a lethal dose of toxin, with undoubted signs of general tetanus, and with the certain fate of death from tetanus in the absence of treatment, and yet some of which at least would not have already fixed in their tissues a lethal dose of toxin, thus rendering them beyond any therapeutic aid. This experiment might have been possible with guinea pigs had we given a smaller and yet a lethal dose of toxin; had we given repeatedly smaller sublethal doses; or had we influenced the character of the disease by a preliminary injection of a quantity of antitoxin insufficient to protect from death but sufficient to induce a milder type of tetanus with a longer period of incubation. We felt, however, that it would be advisable for several reasons to shift our studies to dogs. Of chief importance was the fact that in guinea pigs we have found no demonstrable early infallible sign of general tetanus. By the time we are able to make a certain diagnosis, the animal has generalized rigidity of his voluntary musculature and in all likelihood already has fixed a lethal amount of toxin. In dogs, on the other hand, we have found that wrinkling or furrowing of the brows and erection of the ears in animals having received one or more lethal doses of toxin is an infallible sign of tetanus and that every such animal will become progressively sicker and will die if no treatment is instituted. We have here an early and unmistakable sign comparable to the early trismus in man which so commonly precedes general rigidity or convulsions. Furthermore, the ease and exactness with which antitoxin may be injected into the cisterna is greater in dogs than in guinea pigs.

Experiment 3 (Table III).—Forty-eight hours after the intramuscular injection of 2400 G-P LD50's of toxin per kilogram, all the dogs had

slight local and early general tetanus. They were given varying amounts of antitoxin by intracisternal or intravenous injection. The untreated controls died in from three to five days. The animals which had received 1 and 5 units of antitoxin per kilogram into the cisterna did not survive, although the latter lived three days longer than its mate which received the antitoxin into a vein. All those which received 25 units per kilogram or more in the cisterna lived. Their tetanus progressed rapidly on the day on which treatment was begun and they became so ill and so rigid that they lay prone and could not stand. Complete recovery followed. None of the dogs which received antitoxin intravenously survived.

TABLE III

THE THERAPEUTIC EFFECT OF TETANUS ANTITOXIN GIVEN INTRACISTERNALLY AND INTRAVENOUSLY IN DOGS WITH LOCAL AND GENERAL TETANUS*

AMOUNT OF TETANUS ANTITOXIN IN AMERICAN UNITS PER KG.	ROUTE OF ADMINISTRATION OF ANTITOXIN	
	INTRACISTERNAL	INTRAVENOUS
	RESULT	RESULT
1	Died of tetanus in 6 days	Died of tetanus in 7 days
5	Died of tetanus in 9 days	Died of tetanus in 6 days
25	Severe general tetanus Complete recovery	Died of tetanus in 4 days
125	Severe general tetanus Complete recovery	Died of tetanus in 8 days
625	Severe general tetanus Complete recovery	Died of tetanus in 9 days
Controls. No tetanus antitoxin.		
0	Died of tetanus in 3 days	
0	Died of tetanus in 4 days	
0	Died of tetanus in 5 days	

*Each dog received 2,400 G.P. LD50's of toxin per kilogram intramuscularly. Forty-eight hours later they all had slight local and early general tetanus.† At this time they received varying amounts of antitoxin by the route indicated. Three hours after injection of tetanus antitoxin they all had well-marked general tetanus.

†Wrinkling of brows, erection of ears, stiffness of neck.

NOTE: Autopsies were negative on all of the animals.

Experiment 4 (Table IV).—Nine dogs were given 1200 G-P LD50's of toxin per kilogram intramuscularly. Seventy-two hours later all had slight local stiffness and fairly advanced general tetanus. They were treated at this time. None survived. Those treated by intracisternal injection, however, lived consistently longer than those treated by intravenous injection.

Experiment 5 (Table V).—Twenty-one dogs received 600 G-P LD50's of toxin per kilogram intravenously. Forty-nine hours later they were classified according to severity of symptoms and were treated with 750 American units of antitoxin per kilogram. One animal had no symptoms at this time and was kept as a control. He became prone and had convulsions on the fifth day and died in three weeks. Two other animals with only questionable early symptoms at this time were likewise

TABLE IV

THE THERAPEUTIC EFFECT OF TETANUS ANTITOXIN GIVEN INTRACISTERNALLY AND INTRAVENOUSLY IN DOGS WITH LOCAL AND GENERAL TETANUS*

AMOUNT OF TETANUS ANTITOXIN IN AMERICAN UNITS PER KG.	ROUTE OF ADMINISTRATION OF ANTITOXIN	
	INTRACISTERNAL	INTRAVENOUS
	RESULT	RESULT
140	Died of tetanus in 9 days; right lung consolidated	
700	Died with tetanus in 13 days following gavage and aspiration of vomitus; emaciation; ulceration of mouth	Died of tetanus in 6 days
1400	Died of tetanus in 14 days; emaciation; ulceration of mouth	Died of tetanus in 7 days
2700	Died of tetanus in 14 days; emaciation; ulceration of mouth	Died of tetanus in 8 days

*Each dog received 1,200 G-P LD50's of toxin per kilogram intramuscularly. Seventy-two hours later they all had slight local stiffness and definite general tetanus.† At this time they received varying amounts of tetanus antitoxin by the routes indicated.

†Furrowing of brow, erection of ears, slight trismus, stiffness of neck and trunk, and slight or moderate stiffness of extremities.

NOTE: Autopsies negative except as otherwise stated.

used as controls. They died of tetanus in five and seven days. Of those in the next group with very early tetanus, the one treated by the cisternal route had only slight progression of symptoms and recovered. Of the three treated intravenously, two had slight progression of symptoms, one recovering and one dying of distemper in thirteen days; one became rapidly sicker and died of tetanus in six days. The next group had more advanced signs of early tetanus. The one which received antitoxin into the cisterna had no progression of symptoms and died later of distemper; whereas, one of those treated by intravenous injection showed some progression of symptoms but recovered, and the other became progressively more ill and was sacrificed moribund on the seventeenth day, having extreme tetanus, distemper, and an infected leg. In the next group with more advanced tetanus the one treated by the cisternal method recovered; whereas, the two treated by the intravenous route died of tetanus. The next group had beginning opisthotonos at the time of treatment. Five in which antitoxin was injected into the cisterna had no further progression of symptoms and recovered; whereas, the two having intravenous injection of antitoxin died with tetanus. The one animal with the most advanced tetanus at the time of treatment was given antitoxin intracisternally and died of tetanus in six days.

It will be seen that, if we disregard completely the important factor of the severity of the tetanus at the time of treatment, only 1 of 9 animals given antitoxin intracisternally died of tetanus; whereas, 6 of 9 given antitoxin intravenously succumbed, and all of the untreated

TABLE V

THE THERAPEUTIC EFFECT OF TETANUS ANTITOXIN GIVEN INTRACISTERNALLY AND INTRAVENOUSLY IN DOGS WITH GENERAL TETANUS*

SYMPTOMS AT TIME OF TREATMENT	ROUTE OF ADMINISTRATION OF ANTITOXIN		
	INTRACISTERNAL	INTRAVENOUS	CONTROLS—NO TETANUS ANTITOXIN
	RESULT	RESULT	RESULT
None			D & J† in 5 days; died of tetanus in 21 days; emaciation
Questionable furrowing of brows and erection of ears			D & J in 4 days; died of tetanus in 5 days Body stiff in 4 days; died of tetanus in 7 days
Slight furrowing of brows and erection of ears	Body slightly stiff in 3 days; recovery	Body stiff in 4 days; no further progression; died of distemper in 13 days; pneumonia Body slightly stiff in 4 days; recovery D & J in 5 days; died of tetanus in 6 days	
Erection of ears, furrowing of brows, slight stiffness of neck	No progression of symptoms, died of distemper in 10 days; pneumonia	Neck became more rigid; no further progression; recovery D & J in 5 days; moribund in 17 days; sacrificed; extreme tetanus, distemper, ulcer face, infected leg	
Rather marked stiffness of neck, ears erect, brows furrowed	Body slightly stiff in 3 days; recovery	D & J in 7 days; died of tetanus in 14 days; had distemper; slight consolidation of lung D & J in 5 days; died of tetanus in 18 days	
Ears erect, brows furrowed, body stiff; beginning opisthotonos	No progression; recovery No progression; recovery No progression; recovery No progression; recovery No progression; recovery	D & J in 7 days; died of tetanus in 15 days; had distemper. D & J in 7 days; died of tetanus in 8 days	
Marked stiffness of body	D & J in 4 days; died of tetanus in 6 days		

*Each dog received 600 G-P LD50's of toxin intravenously per kilogram. Forty-nine hours later they were divided into two groups according to symptoms and treated with tetanus antitoxin as indicated. Each received 750 American units per kilogram.

†*D & J* signifies that the animal was prone, unable to stand, and jerking almost constantly in clonic convulsive movements. Autopsies were negative except where otherwise indicated.

controls died. Likewise, it is evident that among those which survived there was less progression of the disease in the animals treated intracisternally.

In this, as in all the other experiments, where any disparity in the signs of tetanus existed at the time of treatment, the animals with the severer signs of tetanus were treated with injection of antitoxin into the cisterna in order to put this mode of treatment to the severer test. In all instances where we have stated the outcome as "died of tetanus" the tetanus had become progressively worse and was so extreme at the time of death that, from our experience, we felt that the dog could not recover regardless of the presence or absence of complications. On the other hand, when an animal is said to have "died of distemper" or from some other cause, the tetanus had been steadily improving before death and it appeared evident that complete recovery would have taken place in the absence of complications. After the single injection of antitoxin all animals were treated exactly alike. Before and after this treatment they were fed the regular laboratory diet of biscuits supplemented with milk and raw ground meat. As soon as they became prone, all were given either daily gavage of sweetened milk or, more commonly, intravenous infusions of normal salt solution and 5 per cent glucose, generally two a day of 100 c.c. each. They were turned frequently. In spite of our efforts most of those lying prone with convulsions for a long time lost weight. Frequently their lips became somewhat ulcerated. Autopsies were done on all. Both intravenous and intracisternal injections were made in unanesthetized animals.

Experiment 6 (Table VI).—This experiment confirms the preceding one. Twenty dogs were given 840 G-P LD50's of toxin intravenously per kilogram. Fifty-two hours later they were grouped according to symptoms and treated with 750 units of antitoxin per kilogram. The one with the mildest symptoms was kept as a control. He died in seven days. In the next group 4 received antitoxin into the cisterna. One died within thirty hours, obviously not of tetanus, and at autopsy showed a hemorrhage in the medulla from inadvertent penetration of the needle during the attempted intracisternal injection and should properly be excluded from the experiment. One in which the tetanus had advanced slightly and then improved steadily, died of distemper. One had no progression of symptoms; one, slight progression. Both recovered. Four treated by intravenous injection exhibited some progression of the tetanus, but 2 recovered, 1 died of distemper, and only 1 died of tetanus. The 2 controls died of tetanus. In the next group 4 received antitoxin by the intracisternal route. The tetanus advanced slightly in 3; 2 recovered, and 1 died of distemper. One became so ill it lay prone with convulsions but recovered completely. Of the 3 treated by the intravenous route, 2 succumbed to tetanus, and 1, which lay prone with convulsions for nearly 2 weeks, eventually recovered. In the last group the dog treated with intracisternal injection of antitoxin developed advanced tetanus but recovered; whereas, its mate treated with intravenous injection died of tetanus.

As in the preceding experiment, if we ignore the degree of tetanus at the time of treatment, none of those given antitoxin into the cisterna

TABLE VI

THE THERAPEUTIC EFFECT OF TETANUS ANTITOXIN GIVEN INTRACISTERNALLY AND INTRAVENOUSLY IN DOGS WITH GENERAL TETANUS*

SYMPTOMS AT TIME OF TREATMENT	ROUTE OF ADMINISTRATION OF ANTITOXIN		
	INTRACISTERNAL	INTRAVENOUS	CONTROLS—NO TETANUS ANTITOXIN
	RESULT	RESULT	RESULT
Beginning erection of ears, furrowing of brows			Body stiff in 4 days; died of tetanus in 7 days
Ears erect, brows furrowed	No progression; recovery	Body stiff in 4 days; recovery	D & J† in 5 days; died of tetanus in 5 days
	Body stiff in 4 days; better in 8 days; recovery	Body stiff in 4 days; recovery	D & J in 4 days; died of tetanus in 5 days
	Body stiff in 4 days; improvement; died of distemper in 10 days; pneumonia; empyema	Body stiff in 4 days; prone in 8 days; died of tetanus in 9 days; slight consolidation one lobe	
	Body slightly stiff in 3 days; dead next A.M.; hemorrhagic tract in medulla from needle trauma	Body stiff in 4 days; died of tetanus in 6 days	
Ears erect, brows furrowed, body moderately stiff	Body stiff in 4 days; better in 6 days; recovery	D & J in 6 days; prone 2 weeks, recovery	
	Body stiff and distemper in 4 days; no progression of tetanus; died of distemper in 9 days; pneumonia; empyema	D & J in 4 days; died of tetanus in 16 days	
	Body stiff in 4 days; recovery	D & J in 4 days; died of tetanus in 18 days	
	D & J in 7 days; up next day; recovery		
Ears erect, brows furrowed, body rather markedly rigid	D & J in 6 days, up next day, recovery	D & J in 3 days; died of tetanus in 5 days	

*Each dog received 840 G-P LD50's of toxin intravenously per kilogram. Fifty-two hours later they were divided into groups according to symptoms and treated with tetanus antitoxin as indicated. Each received 750 American units per kilogram.

†*D & J* signifies that the animal was prone, unable to stand, and jerking almost constantly in clonic convulsive movements. Autopsies were negative except where otherwise indicated.

died of tetanus; whereas, 5 of 8 receiving antitoxin intravenously did die of tetanus.

DISCUSSION

These experiments offer evidence that tetanus antitoxin given intrathecally is much more efficacious as a therapeutic agent in animals which have received more than a lethal dose of tetanus toxin and which have

local or general tetanus than tetanus antitoxin given intravenously. The reason for this is not entirely clear. Ransom[24] claims to have demonstrated that most of the antitoxin introduced intrathecally passes fairly rapidly into the blood stream, although Blumenthal and Jacob[25] state that antitoxin given by subdural infusion remains for at least twenty hours in the cerebrospinal fluid of goats. According to our knowledge of the absorption of cerebrospinal fluid, this is what one should expect. But does some of the antitoxin, perhaps only a small fraction of it, pass directly into the central nervous system? We know that when we inject pontocaine or novocain or some other local anesthetic agent into the subarachnoid space, most of it penetrates directly through the pia and into the substance of the cord, for there follows an anesthetic effect roughly localized to that area of cord with which the solution comes in contact. It may be possible that some of the antitoxin similarly diffuses into the substance of the cord or brain stem. It is true that the molecule of tetanus antitoxin is in all likelihood larger than that of these anesthetic agents. And yet we know that the antitoxin molecule is not too large to pass through the capillary walls of blood and lymph vessels into the various body tissue spaces and vice versa. Until some other explanation is at hand we shall have to assume that it can similarly pass from the cerebrospinal fluid into the substance of the central nervous system.

We have previously pointed out that antitoxin injected directly into the medulla is at least a thousand times more efficacious against toxin previously placed there than is antitoxin injected intravenously. If we can assume then that some of the antitoxin injected into the cerebrospinal fluid, even a small part of it, passes directly into the central nervous system, we can readily understand its greater therapeutic efficacy.

Our experiments do not constitute the first attempt to evaluate the therapeutic effect of intrathecal injections of antitoxin. In 1898 Sicard[26] found that injections of large amounts of antitoxin into the lumbar subarachnoid space of dogs at the onset of symptoms of tetanus would stop the advance of symptoms and save life; whereas, the subcutaneous injection of the same amount was inefficacious. In the same year Blumenthal and Jacob[25] reported that "dural infusion" of antitoxin in goats at the onset of symptoms following the intramuscular injection of several lethal doses of toxin was without effect. In 1914 Permin[27] reported no difference in goats with trismus between the intravenous and intrathecal routes.

On the other hand, Park and Nicoll[28] described at the same time some experiments on guinea pigs which they felt "would seem absolutely conclusive of the superiority of the intraspinal over the intravenous method." Their animals were treated with varying amounts of antitoxin eighteen to twenty-three hours after the intramuscular injection

of 2 M. L. D. of toxin. Their results are similar to those we have reported in Table II. Their intrathecal injections were made in the lumbar space after incision down to the dura, the intravenous injections into the heart. They demonstrated that when the same amount of antitoxin was given it was more efficacious in saving life if given intrathecally than either intravenously or intraneurally and that a smaller dose was efficacious if injected intrathecally rather than by these other routes.

Gottlieb and Freund[29] also found in 1916 that rabbits having received 3 M.L.D. of toxin intramuscularly could not be saved with 1 c.c. of antitoxin given intravenously, even 6 hours after injection; whereas, they could be protected with the same amount of antitoxin given intracisternally up to 25 hours after injection of the toxin.

In 1917 Sherrington's much cited experiments with monkeys were reported.[30] His results may be summarized as follows: All were given approximately 8 lethal doses of toxin intramuscularly. The controls had local tetanus in about 30 to 36 hours, general tetanus by the end of the third day, and died on the fourth or fifth day. Each treated animal received 2,000 American units of antitoxin per kilogram 47 to 78 hours after injection of the toxin. Twenty-five were treated by subcutaneous injection and only 2 survived (tetanus antitoxin 50 and 70 hours after injection); 25 were treated by intramuscular injection with 3 survivals (tetanus antitoxin 47, 50, and 52 hours after injection); 25 were treated intravenously with 7 survivals (tetanus antitoxin 57, 50, 50, 51, 51, 54, and 70 hours after injection); 10 were treated with antitoxin injected under the cerebral dura without any survivals. In contrast to these results, of 25 treated with antitoxin in the lumbar subarachnoid space, 13 survived (tetanus antitoxin 47, 48, 50, 50, 51, 51, 51, 52, 52, 53, 54, 66, 68, and 70 hours after injection) and of 20 treated by the bulbar intrathecal route 13 survived (tetanus antitoxin 47, 48, 50, 51, 52, 53, 56, 66, 66, 68, 70, and 70 hours after injection).

Finally, Florey and Fildes[31] presented some work on rabbits which they felt showed no advantage in the cisternal route. They gave 4 M.L.D. of toxin intramuscularly, a dose found to cause local tetanus in 24 hours and death on the third day. They treated ten rabbits on the second day by operative exposure and injection into the cisterna of 1,000 units of antitoxin and gave simultaneously 15 c.c. of hypertonic salt solution intravenously. They concluded that, when local tetanus was confined to stiffness of the injected leg, all survived, whether treated intravenously or intracisternally, but that when there was the slightest involvement of the head (general tetanus) all died.

It is likely that the good results reported by Roux and Borrel[20] and von Török[32] with antitoxin injected into the cerebrum (a method of administration which obviously cannot be considered in man) are to

be explained on the basis that a large part of the injected antitoxin passes into the ventricular and subarachnoid fluids. Roux and Borrel state that without doubt the injected antitoxin penetrates into the ventricle. Schaeffer and Muckenfuss,[33] using India ink in monkeys, found that the material when injected into the cerebrum reaches the ventricles and subarachnoid space if more than 0.5 c.c. of fluid is injected. Friedmann, Zuger, and Hollander[34] likewise found that dyes injected into the cerebrum passed in large part into the lateral ventricles. Similarly, the occasional good results which have been reported with injection of antitoxin into the sciatic nerve near the sciatic foramen may possibly be due to the forcible injection of antitoxin through the nerve and into the subarachnoid space. For an analysis of the explanation of passage of fluid along nerves into the cerebrospinal fluid, not by any natural pathway, but by forceful driving of the fluid with pressure, see the comments of Abel and his co-workers.[3]

We see, therefore, that most workers have found the intrathecal route to be superior. The failures are, we believe, easy to understand. From our own work it is apparent that, if animals are treated early enough with a sufficient dose of antitoxin, all will survive whether treated by the intrathecal or the intravenous method; and that, conversely, if the treatment is delayed so long that a fatal amount of toxin has been already fixed, antitoxin given by either route will be futile. Furthermore, if one treats animals in between these two periods, that is to say, if they have more advanced symptoms than in the first instance and yet have not undergone fixation of a lethal dose as in the second, success or failure in finding the intracisternal route superior will depend upon varying the dose or upon selecting a proper single dose. Too small a dose may fail to demonstrate a difference between the intrathecal and intravenous routes, as in the animals receiving the smallest doses in the first and second parts of Experiment 1 or in the first pair of dogs in Experiment 3.*

The criticisms which have been made of the experimental demonstration of the superiority of intrathecal injection of antitoxin are well summarized in Huntington's evaluation of Sherrington's work.[15] In the first place, Huntington points out that tetanus toxin and not actual infection with the *Clostridium tetani* was employed. In answer to this criticism it may be pointed out that the pathogenic effect of tetanus infection is manifested only by the toxin and not by the organism per se. The use of tetanus toxin is simply a convenient method of producing tetanus of a measurable degree. In the second place, he points to the enormous dosage of antitoxin which Sherrington used. In other experiments smaller doses have been utilized. In our own experiments with dogs, for example, the 750 units per kilogram used would amount

*The superiority of the intrathecal method was not apparent in our earlier studies and accounts for the incorrect statement made by one of us.[35]

to only 48,750 units in a 65 kilogram man if a comparable amount were given. One would be willing to employ very large amounts of antitoxin if this procedure held any promise of therapeutic benefit. In the third place, Huntington states that man is "vastly" more susceptible to tetanus than is the monkey. As a matter of fact, the consensus is that man is of the same order of sensitivity as the guinea pig and the monkey. It is observed that comparable results with intrathecal injection of antitoxin have been obtained on animals of such diverse sensitivity as the very sensitive guinea pig and monkey and the relatively resistant dog. We have been interested in the behavior of animals of varying sensitivity or resistance to tetanus and conclude that, although different species succumb to widely different amounts of toxin, they all behave similarly as far as their fundamental reaction to tetanus toxin is concerned. Furthermore, we feel that there are only quantitative, not fundamental, differences in the action of tetanus antitoxin on tetanus toxin in the body of both tetanus-sensitive and tetanus-resistant species. Finally, Huntington feels that it is unfair to transfer results from animals suffering from local tetanus alone to man suffering from general tetanus. Our own experiments demonstrate that the same superiority of intrathecal injection of antitoxin holds true with general as well as with local tetanus. It is our feeling that tetanus antitoxin given in proper amount intrathecally will be found superior to antitoxin administered intravenously in any animal poisoned with a lethal quantity of tetanus toxin, with evident symptoms of tetanus, and yet before a fatal amount of toxin has been fixed. We feel that this will hold true for any animal, tetanus-sensitive or tetanus-resistant, including man. We also feel that it will hold true whether the toxin is injected into the body or liberated from tetanus organisms in the body tissue.

For obvious reasons we have purposely omitted reference to clinical reports concerning the relative efficacy of antitoxin given by various routes. With clinical material there is no way of estimating the exact severity of the disease in each instance. The severity of the disease and the prognosis are known to vary with the length of the incubation period, the duration of the disease at the time treatment is begun, the initial symptoms, and other factors. Even if all these data were available in the published reports, and they are not, it would still be difficult to be certain that a group of patients treated in one manner had tetanus of comparable severity with that of a group treated in a different manner. It is a common observation that the mortality from tetanus in any one hospital may vary widely from one period to another, even though the same treatment is used. Furthermore, some of the clinical studies are reported in the literature because the particular treatment employed seemed to have given unusually good results; whereas, reports of other patients treated in the same manner are never published because the outcome has not been so favorable. It appears that the merits

of treatment by intrathecal injection can better be investigated by carefully controlled experimental studies. It is true, of course, that a number of clinicians have differed from the majority all along and have felt that the intrathecal route should be used and that it gives more satisfactory results than do the other methods.

Certain problems remain to be solved. Especially is it important to ascertain whether repeated intrathecal injections are more beneficial than a single one and whether the lumbar subarachnoid route is as efficacious as the cisternal. This work is being pursued. There remains to find out the proper dosage, the number of injections, and the intervals between them which are best suited to the treatment of tetanus.

CONCLUSIONS

1. Experiments are reported which demonstrate that tetanus antitoxin administered intrathecally is superior to that given intravenously in guinea pigs having received more than a lethal dose of tetanus toxin and exhibiting local tetanus, and in dogs poisoned with more than a lethal dose of toxin and showing signs of both local and general tetanus.

2. The significance of these and related experiments is discussed. An explanation of the failure of other workers to demonstrate the superiority of antitoxin administered by intrathecal injection is given.

REFERENCES

1. Bruce, D.: Tetanus. Analysis of 1458 Cases Which Occurred in Home Military Hospitals During the Years 1914-1918, J. Hyg. **19:** 1-32, 1920-21.
2. Abel, J. J.: On Poisons and Disease and Some Experiments With the Toxin of the Bacillus Tetani, Science **79:** 121-129, 1934.
3. Abel, J. J., Evans, E. A., Jr., Hampil, B., and Lee, F. C.: Researches on Tetanus. II. The Toxin of the Bacillus Tetani Is Not Transported to the Central Nervous System by Any Component of the Peripheral Nerve Trunks, Bull. Johns Hopkins Hosp. **56:** 84-114, 1935.
4. Abel, J. J., Hampil, B., and Jonas, A. F., Jr.: Researches on Tetanus. III. Further Experiments to Prove That Tetanus Toxin Is Not Carried in Peripheral Nerves to the Central Nervous System, Bull. Johns Hopkins Hosp. **56:** 317-336, 1935.
5. Firor, W. M., and Jonas, A. F., Jr.: Researches on Tetanus. VI. Production of Reflex Motor Tetanus by Intraspinal Injection of Tetanus Toxin, Bull. Johns Hopkins Hosp. **62:** 91-109, 1938.
6. Abel, J. J., Firor, W. M., and Chalian, W.: Researches on Tetanus. IX. Further Evidence to Show that Tetanus Toxin Is Not Carried to Central Neurons by Way of the Axis Cylinders of Motor Nerves, Bull. Johns Hopkins Hosp. **63:** 373-403, 1938.
7. Abel, J. J., Evans, E. A., Jr., and Hampil, B.: Researches on Tetanus. V. Distribution and Fate of Tetanus Toxin in the Body, Bull. Johns Hopkins Hosp. **59:** 307-391, 1936.
8. Firor, W. M., and Lamont, A.: The Apparent Alteration of Tetanus Toxin Within the Spinal Cord of Dogs, Ann. Surg. **108:** 941-955, 1938.
9. Harvey, A. M.: The Peripheral Action of Tetanus Toxin, J. Physiol. **96:** 348-365, 1939.
10. Firor, W. M., Lamont, A., and Shumacker, H. B., Jr.: Studies on the Cause of Death in Tetanus, Ann. Surg. **111:** 246-274, 1940.
11. Von Behring, E.: Indikation für die Serumtherapeutische Tetanusbekämfung, Deutsche med. Wehnschr. **40:** 1833-1834, 1914.
12. Abel, J. J., Hampil, B., Jonas, A. F., Jr., and Chalian, W.: Researches on Tetanus. VII. The Time Required for the Fixation of a Fatal Quantity of Tetanus Toxin, Bull. Johns Hopkins Hosp. **62:** 522-563, 1938.

13. Abel, J. J., and Chalian, W.: Researches on Tetanus. VIII. At What Point in the Course of Tetanus Does Antitetanic Serum Fail to Save Life? Bull. Johns Hopkins Hosp. **62**: 610-633, 1938.
14. Shumacker, H. B., Jr., Firor, W. M., and Lamont, A.: Toxin Antitoxin Reactions in Experimental Tetanus, Bull. Johns Hopkins Hosp. In press.
15. Huntington, R. W., Jr.: The Treatment of Tetanus, Yale J. Biol. & Med. **3**: 207-233, 1931.
16. Annex 1 A. The Assay of Tetanus Antitoxin. League of Nations Bull. Health Organization **7**: 713-732, 1938.
17. Sordelli, A.: Annex 1 B. Assay of Three Tetanus Antitoxins, League of Nations Bull. Health Organization **7**: 733-738, 1938.
18. Smith, M. L.: The Standardization of Tetanus Antitoxin. Factors Influencing the Assay, League of Nations Bull. Health Organization **7**: 738-769, 1938.
19. Courmont, J., and Doyon, M.: Le Tétanos, Paris, 1899.
20. Roux, E., and Borrel, A.: Tétanos cérébral et immunité contre le tétanos, Ann. l'Inst. Pasteur **12**: 225-239, 1898.
21. Meyer, H.: Tetanus Studien, Chemische und medicinische Untersuchungen, Braunschweig 1901, Festschrift f. Max Jaffe, pp. 295-317.
22. Shumacker, H. B., Jr., Lamont, A., and Firor, W. M.: The Reaction of "Tetanus-Sensitive" and "Tetanus-Resistant" Animals to Injection of Tetanal Toxin into the Spinal Cord, J. Immunol. **37**: 425-433, 1939.
23. Wolff-Eisner, A.: Die Bindungverhältnisse der Organgewebe gegenüber Toxinen und ihre klinische Bedeutung für Inkubation und natürliche Immunität, Centralbl. f. Bakt. **47**: 213-237, 1908.
24. Ransom, F.: Die Injection von Tetanustoxin bezw. Antitoxin in den subarachnoidalen Raum, Ztschr. f. physiol. Chem. **31**: 282-304, 1900-01.
25. Blumenthal, F., and Jacob, P.: Zur Zerumtherapie des Tetanus. Berl. klin. Wchnschr. **35**: 1079-1080, 1898.
26. Sicard, M. A.: Toxine et anatoxine par injectionssous-arachnoïdiennes, Compt. rend. Soc. de biol. **50**: 1057-1058, 1898.
27. Permin, C.: Experimentelle und klinische Untersuchungen über die Pathogenese und Therapie des Starrkramfes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**: 1-21, 1914.
28. Park, W. H., and Nicoll, M.: Experiments on the Curative Value of the Intraspinal Administration of Tetanus Antitoxin, J. A. M. A. **63**: 235-238, 1914.
29. Gottlieb, R., and Freund, H.: Experimentelle Studien zur Zerumtherapie des Tetanus, Münch. med. Wchnschr. **63**: 741-746, 1916.
30. Sherrington, C. S.: Observations With Antitetanus Serum in the Monkey, Lancet **2**: 964-966, 1917.
31. Florey, H., and Fildes, P.: Tetanus VII. The Treatment of Tetanus in Rabbits by Large Intrathecal Doses of Antitoxin, Brit. J. Exper. Path. **8**: 393-397, 1927.
32. Von Török, A.: Experimentelle Beiträge zur Therapie des Tetanus, Ztschr. f. Heilk. **21**: 54-172, 1900.
33. Schaeffer, M., and Muckenfuss, R. S.: The Distribution of Material Following Intracerebral Inoculation Into Macacus Rhesus Monkeys and Its Possible Influence Upon the Results of Neutralization Tests in Experimental Poliomyelitis, Am. J. Path. **14**: 226-236, 1938.
34. Friedmann, U., Zuger, B., and Hollander, A.: Quantitative Studies on the Neutralization of Pathogenic Agents in Tissues by Circulating Antitoxin. III. The Permeability of the Cerebral Capillaries to Antibodies, J. Immunol. **36**: 219-230, 1939.
35. Firor, W. M.: The Prevention and Treatment of Tetanus, Am. J. Surg. **46**: 450-453, 1939.

THE PANCREATICOHEPATIC SYNDROME

Pancreatic Fibrosis and Fatty Liver

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WHEN Fisher[1] and Allan and associates[2] (1924) discovered that pancreatectomy in the dog led to fatty infiltration of the liver and death of the animal in two to eight months, they laid the foundation for the recognition of a human clinical syndrome consisting primarily of an atrophy or sclerosis of the pancreas with fatty infiltration of the liver. Insulin, of course, was given to the animals to prevent diabetes. Allan and his co-workers noted that insulin removed the fat in the liver which might be deposited within a few days following the pancreatectomy but that the fatty infiltration would recur weeks later. These same authors also noted that the addition of raw pancreas to the diet of these dogs would prevent the deposition of fat in the liver. A few years later Hershey and Soskin[3] noted that the addition of lecithin (as obtained from egg yolk) to the diet of pancreatectomized dogs would also prevent death from fatty infiltration of the liver. A year or two later Best, Ferguson, and Hershey[4] showed that the action of lecithin in the prevention of fatty liver was most likely due to the choline contained in it.

Perhaps the most important contribution to the phenomenon of fatty liver in pancreatic insufficiency was made by Dragstedt and associates[5] in 1936. They made an alcoholic extract of beef pancreas which, when given to pancreatectomized dogs, would prevent the fatty liver. They have called this substance lipocaic. Best and Ridout[6] tried lipocaic preparations made after the method of Dragstedt and associates and concluded that the effectiveness was perhaps due to the choline and other unknown factors in the proteins contained in the lipocaic extract, although they admit that the "extract contains only small quantities of choline." In a recent article Dragstedt[7] appears to have demonstrated satisfactorily that the effectiveness of lipocaic is not due to the choline contained in it. Dragstedt states that "it requires approximately 2 grams of choline a day over and above that present in the diet to exert this beneficial effect, whereas 100 grams of pancreas, which is an effective dose, contains only about 250 mg. of choline." He notes also that "liver and brain which contain as much or more lecithin and choline, exert no beneficial effect."

The next problem in the study of the mechanism of production of fatty liver by pancreatectomy lies in the question of whether the action is due to the loss of the internal or external secretion. Elman and McCaughan[8] and others have called attention to the importance of the ex-

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ternal secretion of the pancreas to the well-being of the animal. Berg and Zucker[9] obtained fatty changes in the liver of dogs which survived eighty days or longer following diversion of the external secretions to the outside. However, Dragstedt and associates[10] could not duplicate the findings and concluded that neither loss of external secretion by pancreatic fistula nor ligation of all the pancreatic ducts would result in the type of fatty liver as noted following pancreatectomy. In a more recent publication Dragstedt[7] implies that the factor preventing the fatty liver must be a second component of internal secretion, particularly since feeding of pancreatic juice does not prevent the fatty infiltration, even though it does improve the digestion and absorption of food.

RELATIONSHIP OF PANCREATICOHEPATIC SYNDROME TO OTHER DISEASES

Up to the present time there are relatively few of the "typical" type of fatty liver and pancreatic atrophy reported in adults (six, including the one herein described). However, there are several allied diseases which bear a direct resemblance to the syndrome. Perhaps the condition bearing the most resemblance is childhood pancreatic steatorrhea which has had the terms cystic fibrosis of the pancreas, congenital steatorrhea, etc., applied by various authors. It is our opinion that this disease is identical to the one under discussion in this report, with one notable exception; namely, that it occurs in childhood, whereas the other group occurs in adults.

Andersen[11] has recently made a study of forty-nine cases (as collected from various sources) of fibrosis of the pancreas in infants and children. She noted that in nineteen instances fatty infiltration of the liver existed. Of more importance was the fact that 60 per cent of the patients in the older group, i.e., from 6 months to 14½ years of age, had fatty infiltration of the liver. In animals we know that it takes several weeks or months for pancreatic deficiency to produce a fatty liver and that in human beings it presumably takes even longer. It is therefore obvious that the absence of a fatty liver in an infant only a few months old does not exclude the disease. Clinical manifestations as noted by Andersen and others include malnutrition, frequent bulky foul stools after the age of 6 months, protuberant abdomen, anemia, muscular weakness, and mild osteoporosis, all of which are manifestations similar to those described in celiac disease. Not all instances of fibrosis of the pancreas have the bulky, fatty, foul-smelling stool even though the process has advanced to the stage where fatty infiltration of the liver is advanced. This is illustrated by a case (patient aged 4 years) reported by Davie.[12] Bronchiectasis and pneumonia are common in pancreatic steatorrhea of childhood; death is almost always secondary to or accompanied by the latter.

In spite of the similarity of congenital pancreatic steatorrhea to celiac disease, there are a few points of dissimilarity. These have been summarized by Harper[13] as follows (Table I):

TABLE I

CONGENITAL PANCREATIC STEATORRHEA	CELIAC DISEASE
Symptoms since birth	Onset 9 months to 2 years
Oil present in stool	Oil not present in stool
High fecal fat; large amount unsplit	High fecal fat; well split
Glucose tolerance curve on high side of normal	Glucose tolerance curve flat
Post mortem shows lesion in pancreas	Post mortem shows no lesion in pancreas

However, it should be stated that there is not a complete agreement (Hess and Saphir[14]) as to the definition of the term celiac disease, particularly as to the absence of a pathologic lesion in the pancreas. With the exception of the points mentioned above, the symptoms and physical findings of pancreatic steatorrhea are identical to those in nonpancreatic steatorrhea (celiac disease). The chief differences therefore lie in the pathologic findings in the pancreas and the type of fat in the stool; i.e., the amount of neutral fat and fatty acids. The numerous points of similarity suggest therefore that the two diseases may be the same except that celiac disease is an earlier stage or is an expression of the results of pancreatic dysfunction in the absence of demonstrable pathologic changes in the organ.

Another disease with evidence of pancreatic dysfunction as evidenced by fatty diarrheal stools is sprue. Writers on the subject have been inclined to divide the disease into two divisions, tropical and nontropical sprue; but in a recent study Snell[15] finally concludes that the two diseases are the same. He remarks that nontropical sprue may represent a more advanced stage of the disease largely through delay in diagnosis. However, since pancreatic lesions are absent in each group and pancreatic enzymes are found in the duodenum, it appears likely that sprue and the pancreaticohepatic syndrome (pancreatic steatorrhea) are not identical. However, the manifestations of sprue including glossitis, stomatitis, anemia, fatty diarrhea, emaciation, low blood calcium, low blood protein, osteoporosis, low blood cholesterol, etc., are remarkably similar to those found in pancreatic steatorrhea. The great difference lies in the fact that in sprue anemia is more pronounced and is relieved by liver therapy. Sprue therefore might be considered an intermediary disease between pernicious anemia and pancreatic steatorrhea.

ETIOLOGY

After reviewing the cases of fatty infiltration of the liver secondary to pancreatic dysfunction (with pathologic confirmation in the pancreas), it appears that the disease described in childhood as pancreatic steatorrhea and the disease more recently described in adults with fatty liver and pancreatic sclerosis are the same. However, the etiologic factor and pathogenesis of the pancreatic disease may be slightly different. In childhood Andersen[11] has suggested three possible etiologic factors for the pancreatic fibrosis: (1) congenital malforma-

tion of the ducts, (2) inflammation of the pancreas in fetal life, and (3) vitamin A deficiency. In adults it likewise appears that several factors are possible.

Although there have been cases reported with post-mortem findings in which pancreatic disease and fatty liver were noted along with other findings (Choy and Oh,[16] Paviot and associates,[17] and others), Snell and Comfort[18] were perhaps the first to emphasize the importance of the pancreatic lesion in the production of the fatty liver, particularly as a corollary to the production of fatty infiltration of the liver to pancreatectomy in dogs.

Up to the present time there are reports of six cases in the literature, including the one herein discussed. Three were reported by Snell and Comfort. In the case herein reported it appears that gall bladder disease was perhaps the primary cause of the severe fibrosis and atrophy of the pancreas, aided perhaps by an old penetrating duodenal ulcer. The presence of gall bladder disease (with stones) in Rosenberg's[19] case, along with a possible cholecystitis in two of the other four cases, suggests that gall bladder disease may be an important etiologic factor. The importance of this possible relationship becomes more apparent when we recall that the gall bladder is diseased (usually with stones) in such a large percentage of patients with acute pancreatitis and is probably the direct etiologic factor in the development of the pancreatitis. In two of Snell's patients pancreatic lithiasis appears to have been the cause of the pancreatic fibrosis with insufficiency, but the cause of the pancreatic stones is, of course, obscure. In the case reported by Norris, Beard, and Gerber,[20] a small carcinoma was found in the head of the pancreas. Whether or not this could have been responsible for the severe grade of pancreatic atrophy is not certain. Even if it is assumed that the tumor was compressing the duct of Wirsung, would this be sufficient to cause atrophy and fibrosis because of obstruction of the duct over such a short time? It appears doubtful.

It becomes obvious then that more cases will have to be studied before any conclusion may be reached as to the predominating etiologic factor causing the pancreatic lesion. The recent experiments of Chaikoff[21] suggest that vitamin deficiency may be an important factor in the development of the disease so far as he has been able to keep two dogs alive for at least four years after pancreatectomy when they were fed vitamins A, B, and D along with lean meat, sucrose, and bone ash. In children Andersen[11] has suggested that vitamin A deficiency may be an important factor in the etiology. The other two possible factors suggested by Andersen were congenital malformation (duct obstruction) and fetal acute pancreatitis.

It, therefore, appears safe to assume that the fatty infiltration of the liver is always secondary to a severe pancreatic insufficiency incident to pancreatic atrophy and fibrosis. Undoubtedly, the pancreatic fibrosis may be caused by numerous factors as described above, including any

process which may obstruct the ducts. There appear to be enough clinical data to support this assumption, in spite of the fact that simple ligation of the ducts in dogs will not produce a typical fatty liver. The difference may be in the fact that in operative ligation of ducts there is no accompanying infection; whereas, in human beings the process producing the obstruction (even if stones) is apt to be accompanied by infection. Another important feature may lie in anatomical variations, so far as obstruction of the duct of Wirsung would obviously be most damaging in the instances when the accessory duct was poorly developed or not anastomosing with the duct of Wirsung. In the average pancreas (human and dog) there is a certain amount of anastomosis between the two duct systems.

CLINICAL MANIFESTATIONS

A study of the five adult cases previously reported by various authors and the one herein discussed reveals the fact that the manifestations are extremely variable. The duration of symptoms likewise varies from eight months to twenty years, depending upon the cause. Conforming to the definition of the disease requiring pancreatic fibrosis and fatty infiltration of the liver as prerequisites, the manifestations will consist largely of symptoms produced by lesions of these organs. However, it is a notorious fact that symptoms produced by diseases of these two organs are insidious and extremely varied. The fact that other organs are likely to be affected in a functional way in the absence of pathologic lesions is bound to add to the inconsistencies in the manifestations. The disease attacks males equally as often as females; in adults it may be encountered in any decade.

One of the earliest manifestations is the passage of frequent, foul, fatty, bulky stools. However, in two of the six adult cases available for study, stool changes were insignificant. One of the most common complaints is weakness. Loss of weight may occur, but two of the six cases were obese. Anorexia, nausea, and vomiting are frequent and may occur in attacks with or without abdominal pain. Mild pain and discomfort in the epigastrium related presumably to the pathologic changes in the liver and pancreas are common. When the pancreatic lesion is secondary to gall bladder disease, there may naturally be attacks of severe pain located particularly in the right upper quadrant.

Obviously the size of the liver will depend upon the amount of fat contained in it. In the case herein reported the liver extended down about 6 cm. Various tests of hepatic function, including the hippuric acid and bromsulphalein tests, have been positive; as would be expected, the blood protein may likewise be lowered (Table II).

Cardiac manifestations, including dyspnea, etc., have been noted at times and in the case herein reported were substantiated by severe fatty changes in the myocardium (see autopsy protocol, case report). Hypertension has been noted on only one occasion and is perhaps coincidental.

TABLE II

SUMMARY OF CASES REPORTED AS PANCREATICOHEPATIC DISEASE*

AUTHOR	SEX	AGE	LIVER	PANCREAS	GALL BLADDER DISEASE	RED COUNT MILLION	BLOOD PROTEIN GM. %	BLOOD CHOLESTEROL MG. %	DIARRHEA	STOOL	ASCITES ED. EXT	RESULT
Snell and Comfort	M	36	Fatty	Stones	-		7.2	192	+	Fatty, foul	+	Well, lipocaic
Snell and Comfort	M	40	Fatty	Stones	+	4.2	Albumin 2.9 Globulin 2.7	89	+	Fatty, foul	+	Improved
Snell and Comfort	M	62	Fatty	Multiple cysts	?	3.7	Albumin 1.4 Globulin 2.2	75	+	Fatty, foul	+	Died, autopsy
Norris and associates	F	68	Fatty	Fibrosis, atrophy	+ ?	5.0 *down to* 3.6			+	Fatty, foul	+	Died, autopsy
Rosenberg	F	59	Fatty	?	+	4.1		176	-	-	-	Well, lipocaic
Cole and Howe	F	30	Fatty	Fibrosis, atrophy	+	3.6	Albumin 2.0 Globulin 2.1	135	-	-	-	Died, autopsy

*To be complete this summary should also include cases of pancreatic steatorrhea of infancy and childhood, such as those recently summarized by Andersen.[11]

Although two of the six cases studied were obese, this feature may also be coincidental; both of these cases had hirsutism. Ascites and edema of the extremities have been noted too often to be of only coincidental significance. Since renal damage has been insignificant in all cases studied, the causative factors of the ascites would appear to be the heart and liver. Only two of the six cases had diabetes. In view of the fact that pancreatic destruction may be so pronounced, one might expect diabetes to be observed more commonly. However, when we consider that the glycosuria or diabetes accompanying the destructive types of acute pancreatitis is mild and commonly absent, the infrequency of diabetes in pancreaticohepatic disease is not inconsistent. Apparently the viability of relatively few islands of Langerhans is sufficient to prevent diabetes.

Laboratory tests, in addition to the liver function tests and urine examination previously mentioned, may be helpful. Snell and Comfort[18] call attention to the absence or diminution of pancreatic enzymes in the duodenal secretion. On two occasions there has been no free hydrochloric acid in the stomach. This finding may be of considerable significance because gastric analysis was not performed on all the cases studied. Anemia appears to be a fairly constant finding, being observed in four of six cases. The serum amylase in our case was very low before operation, but was elevated above normal after operation. The low reading was presumably an expression of hepatic insufficiency; Somogyi[22] has called attention to this relationship, a finding which we have been able to corroborate. The blood cholesterol is usually lower than normal. As stated, there seems to be a definite tendency toward a lowering of the blood protein level, with a shift toward reversal of the albumin-globulin ratio. According to the experience of Keeton and his associates[23] and others, this would be corroborative evidence toward the existence of hepatic insufficiency.

A study of the manifestations encountered in the so-called pancreaticohepatic syndrome shows a definite similarity to those described years ago (1923) by Whipple[24] as pancreatic asthenia. However, he was describing an acute condition observed as a postoperative complication. For example, the anorexia, nausea, vomiting, apathy, and loss of weight are symptoms in common. In his group he noted a lowering of blood pressure and occasionally a tendency toward hemorrhage. Glycosuria was not significant.

The symptoms of pancreatic steatorrhea of infancy and childhood, as noted previously, consisting primarily of steatorrhea, diarrhea, loss of weight, anemia, protuberant abdomen, mild osteoporosis, and tendency to bronchiectasis and pneumonia, are remarkably similar to the symptoms herein discussed as belonging to the pancreaticohepatic syndrome. Points of difference consisting, for example, of mild osteoporosis would be readily explained because of growth requirements in children.

Higher vitamin requirements in children would explain the higher incidence of pulmonary infection in children, if Andersen's[11] suggestion that the pulmonary infection in pancreatic steatorrhea is secondary to a vitamin deficiency is correct.

Therefore, it is our opinion that the pancreatic fibrosis and fatty liver (pancreaticohepatic syndrome) in adults is the same disease as pancreatic steatorrhea (congenital steatorrhea) in infancy and childhood. Differences in the clinical picture of the two conditions are readily explained by the influence of growth requirements in childhood. The pathologic features are even more similar, particularly if we realize that it takes several months for significant fatty infiltration of the liver to take place; we would therefore not expect much fat in the liver of an infant succumbing to the disease at an age under 6 months.

TREATMENT

In view of the splendid contributions of Dragstedt and associates,[5, 7, 10] one of the most important features in treatment would certainly lie in lipocaic therapy. The prevention of death following pancreatectomy in dogs by feeding vitamins A, B, and D, as noted by Chaikoff,[21] is in itself sufficient evidence to justify vitamin therapy. Utilization of high carbohydrate and protein diets as indicated may be helpful. The caloric intake should be 20 to 25 per cent above the average requirement, because of the loss of such a large amount of fat in the stool. The use of salyrgan and other drugs should be utilized in symptomatic therapy as indicated. The above remarks on therapy apply also to pancreatic steatorrhea of childhood, particularly the lipocaic therapy. As a matter of fact, on theoretical grounds lipocaic therapy would appear also to be indicated in the idiopathic types of steatorrhea (e.g., celiac disease) since there is presumably pancreatic dysfunction in that group.

REPORT OF CASE

Patient M. R. (No. 56711) was a female 30 years of age, who entered the hospital Sept. 10, 1937, complaining particularly of vomiting of eight weeks' duration. She stated that beginning in about 1922 she developed discomfort in the epigastrium associated with occasional vomiting. Vomiting and discomfort occurred particularly one or two hours after meals. In 1925 the patient had an appendectomy without improvement. Vomiting offered relief. Symptoms became worse until 1930 when she came to Illinois Research Hospital. Gastric analysis at this time revealed total acidity of 50, being elevated to 60 with an Ewald meal. On May 14, 1930, the patient had a laparotomy, at which time a duodenal ulcer was found. The ulcer was annular, stenosing the duodenum and invading the pancreas. A Billroth II type of resection was performed. For two years following operation the patient was completely well. In 1932 she had a severe gastric hemorrhage, but she has had none since. For the past two years she has had intermittent gnawing pain in the epigastrium with occasional attacks of vomiting; this pain radiates to the left and posteriorly, suggesting that it might be of pancreatic origin. Pain is relieved somewhat by alkalies. Ordinarily vomiting relieved the pain, but recently it has not relieved the discomfort which had been even more distressing during the past two months.

Examination of the abdomen revealed a large mass in the right upper quadrant, extending down about 6 cm. below the costal margin. There was moderate tenderness over this mass which presented a smooth surface. Mild hirsutism was present. Her height was 5 feet, 6 inches; weight was 185 pounds. Gastrointestinal series

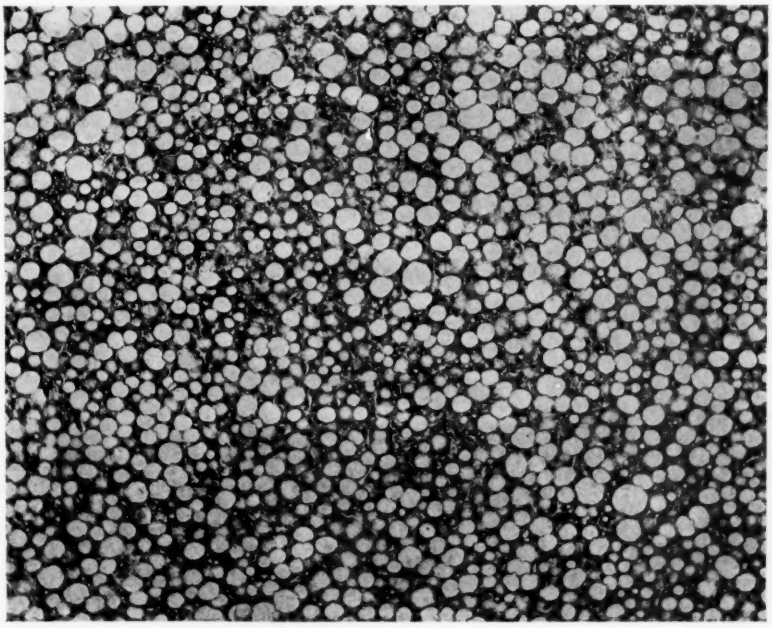

Fig. 1.—Low-power photomicrograph of liver, showing marked fatty infiltration and degeneration. Not enough hepatic cells remain to identify the tissue as liver.

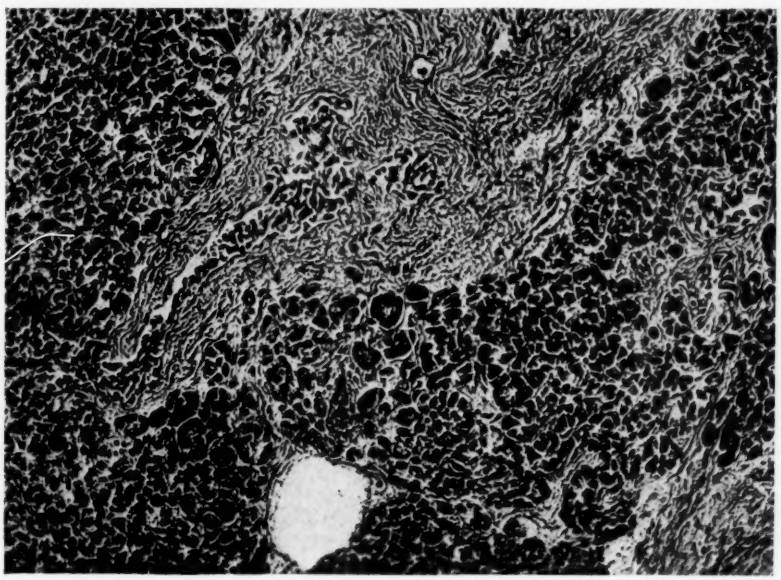

Fig. 2.—Photomicrograph of pancreas, low power, showing distortion of acinar structure with interacinar and intercellular fibrosis. Many cells show degenerative changes and there are several large fat vacuoles present. The picture is one of atrophy and fibrosis.

revealed a gastroenterostomy stoma functioning well. There was no six-hour retention. Cholecystogram revealed no shadow, indicating a pathologic gall bladder. Blood pressure was 125/85. The red blood cell count was 3,600,000. The Kahn test was negative. The fasting blood sugar was 81, N.P.N. 27 and blood chlorides 427. On admission, the patient's serum amylase was 13 (normal 100 to 150). After operation it rose to 255, suggesting that in some way there had been a reactivation of the inflammatory process in the pancreas. The serum albumin was 2 and the serum globulin 2.1, revealing a low albumin level with a tendency to reversal of the albumin-globulin ratio. The icterus index and serum bilirubin were two or three times normal, being 11 and 0.7 respectively. The blood cholesterol was 135 mg. per cent.

Because of the presence of the mass and symptoms, operation was advised and performed on Sept. 20, 1937. The gall bladder was buried in adhesions and contained numerous stones. The liver was enlarged down to the umbilicus, but it had a smooth surface. It was yellowish white in color and, except for position, could not have been identified as liver. Examination of the stomach revealed the closed pyloric end and a gastroenterostomy conforming to the history of a Billroth II operation performed previously. There were numerous adhesions in the region of the stoma which included the colon and some loops of upper ileum. It appeared that a gastrocolic fistula was perhaps present, but in view of lack of accurate conformation it was decided not to do anything about it at this time. Realizing that the patient was probably suffering from fatty liver resulting from pancreatic damage, we directed our attention to relieving the pancreas, if possible. Because of the relationship of gall bladder disease to pancreatitis, we decided to remove the badly diseased gall bladder, containing stones. This was done, and the wound closed after a biopsy of the liver was taken. The patient made a rather uneventful convalescence following operation and was allowed up on the sixteenth day. Shortly after being up, she complained of dyspnea and precordial pain. She was put to bed, but dyspnea, cyanosis, and tachycardia persisted in spite of therapy and the signs of acute myocardial failure persisted until her death a few days later, Oct. 10, 1937.

Autopsy Protocol.—The autopsy was performed approximately ten hours after death.

The body was that of a well-developed, moderately obese white woman, 30 years of age, measuring 65 inches in length and weighing 175 pounds. The skin and mucous membranes were a normal color. There was no cyanosis or icterus. There was a slight pitting edema of the lower extremities.

The abdomen was distended. There was a recently healed right pararectus incision 23 cm. in length. The peritoneal cavity contained only a few cubic centimeters of fluid. The intestines were distended and in several places showed perforations, obviously post mortem due to autolysis. The omentum was adherent to the parietal peritoneum at the site of the surgical incision and also to the gall bladder bed. There was no fluid in either pleural cavity and only a few cubic centimeters of clear straw-colored fluid in the pericardial sac. There were no adhesions in the left pleural cavity. In the right pleural cavity there were old fibrous adhesions particularly dense over the lower lobe.

The heart weighed 295 Gm. The subepicardial fat was markedly increased in amount. The myocardium was light yellowish brown, rather soft and flabby, and on the endocardial surface had a mottled yellow "faded leaf" appearance. The right ventricular wall averaged 3 mm. in thickness, but in some areas was thinned to 1 mm. of muscle, while the remainder of the wall consisted of fat. The valve leaflets were normal. The coronary arteries and root of the aorta showed a few scattered fatty plaques measuring up to 2 mm. in diameter.

The lungs were crepitant throughout. Their cut surfaces were moist and reddish purple in color. The larger bronchi contained a small amount of frothy mucus.

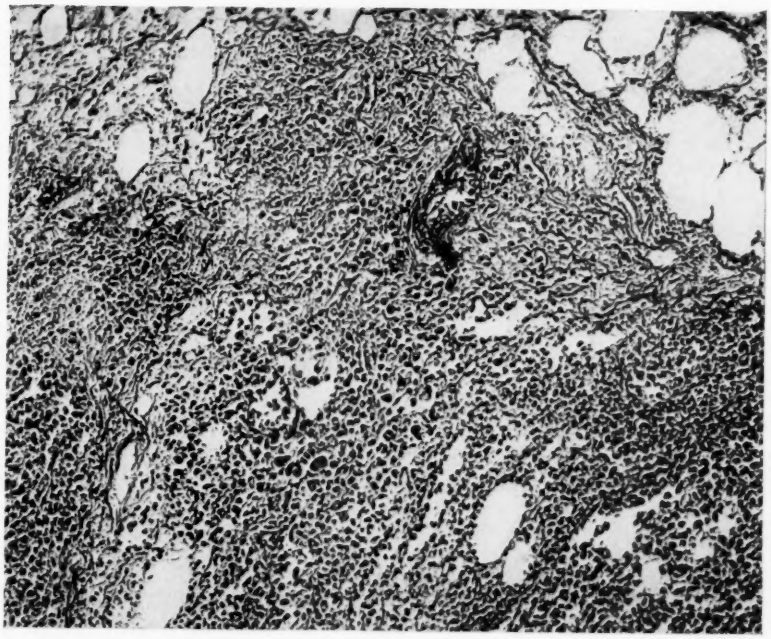

Fig. 3.—Low-power photomicrograph of pancreas, showing necrosis and degeneration of the acinar tissue. The necrosis is so extensive that all cellular detail is lost. In many instances the nucleus is the only structure remaining as identifiable.

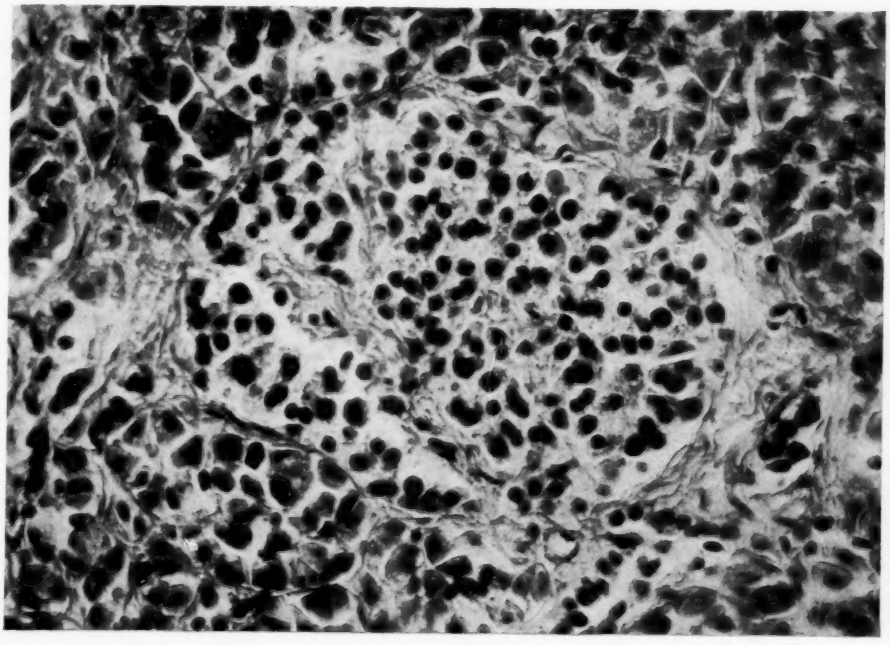

Fig. 4.—High-power photomicrograph of pancreas, showing a relatively normal island of Langerhans. There did not appear to be any significant decrease in the islands, presumably because the islands were more resistant to the necrotizing process.

The liver weighed 4,410 Gm. and was uniformly enlarged to almost three times the normal size. It was firm, finely nodular, light yellowish brown in color, and on cut section the lobular markings were indistinct. The gall bladder had been surgically removed.

The spleen weighed 275 Gm. On section it was soft in consistency, the cut edges everted, and the pulp scraped with moderate ease. The color was reddish purple and the trabeculae and follicles were distinct.

The pylorus was closed by an old operative procedure and there was a patent stoma of a posterior gastrojejunostomy. The transverse colon was closely adherent to the stomach at the site of the gastrojejunostomy. There was a jejunocolic fistula which easily admitted a finger. The stomach contained intestinal contents of a fecal type. There was no evidence of a gastric or jejunal ulcer on careful examination. The remainder of the intestinal tract was normal except for autolytic changes.

The pancreas weighed 49 Gm. and was definitely decreased in size. It was soft, light yellow, and lobulated. Scattered throughout the pancreas were firm white patches measuring up to 3 mm. in diameter.

The kidneys together weighed 375 Gm. The capsules stripped with ease, leaving smooth surfaces. On cut section they were soft and pasty pinkish gray, and the cortical striations were indistinct. In the left kidney there was a bilocular subcapsular cyst filled with clear fluid.

The uterus and adrenals were entirely normal.

Both ovaries showed a few simple cysts, measuring up to 3 mm. in diameter.

Microscopic sections of liver showed the structure almost completely obscured by large vacuoles in the parenchymal cells, so that from the microscopic structure it was difficult to recognize the section as liver. The fat vacuoles were uniformly distributed throughout the section, and sections from different parts of the liver had an identical appearance. In some areas there was a moderate accumulation of small round cells in the portal space.

Microscopic sections of the pancreas from three different areas showed a varying picture. In the white patches described grossly the tissue was entirely necrotic. The nuclear outlines of the acinar cells had completely disappeared and only a dim shadow of the cell structure remained. In other areas the acinar structure was distorted and the individual cells separated by fibrous tissue. Many cells showed atrophic and degenerative changes. There was an increased number of fat cells in the connective tissue stroma. The islets of Langerhans, for the most part, were well preserved and showed less pathologic change than did the acinar tissue. Sections of spleen and adrenal showed no important pathologic changes.

The pathologic diagnosis was: (1) Marked fatty metamorphosis of the liver; (2) fatty infiltration of the myocardium; (3) focal necrosis, atrophy, and fibrosis of the pancreas; (4) old gastrojejunostomy; (5) jejunocolic fistula at the site of the gastrojejunal stoma; (6) healed cholecystectomy; (7) old fibrous adhesions between omentum, parietal peritoneum, and gall bladder bed; (8) parenchymal degeneration of the kidneys; (9) subcapsular cyst of left kidney; (10) old fibrous pleuritis, right.

COMMENT

In our case the fatty infiltration of the liver and the pancreatic fibrosis had progressed to an advanced degree (weight of liver 4,400 Gm.). The immediate cause of death was myocardial decompensation as supported by replacement of heart muscle by fat to such a degree that in places the myocardium was no thicker than 1 mm. In spite of the severe degree of pancreatic destruction, the patient did not have the typical fatty foul stool exemplifying the disease. The etiologic factor causing the

pancreatitis is not clear, but presumably it was gall bladder disease including cholelithiasis. Although a jejunocolic fistula existed, it is difficult to see how this lesion could possibly have been a significant factor in the pathogenesis of the pancreatitis, particularly since considerable space intervened between the fistulous mass and the pancreas. There is much more experimental evidence to point toward a lymphatic communication between the gall bladder and pancreas than there would be between the pancreas and an inflammatory mass such as that produced by the jejunocolic fistula found in this patient. It is perhaps difficult to explain why there should be such extensive fatty degeneration of the myocardium in a patient only 30 years of age. There was clinical evidence of hepatic insufficiency as borne out by the low serum amylase on admission, a decreased serum albumin with reversal of the albumin-globulin ratio, and a terminal subclinical icterus. The fasting blood sugar was 80 mg. per cent and the urine was negative for reducing sugars. This corresponds well with the histologic observation that the islets of Langerhans were little involved by the necrosis and fibrosis, as well as with the well-known fact that diabetes is rarely the sequel of pancreatitis, even when severe and causing extensive destruction of the pancreas.

The question of the relation of the type and extent of pancreatic pathology to lipocaic deficiency is interesting. Dragstedt,[7] on the basis of experimental work, suggests that lipocaic may be elaborated by the alpha cells of the islets of Langerhans and that the lipocaic-deficiency syndrome should be fairly common in diabetics. Rosenberg has reported a clinical case of fatty liver with deficient function occurring in a diabetic and improved by the administration of lipocaic. It is of interest, however, that his patient had gall bladder colic and was operated upon for hydrops of the gall bladder. Although it is a well-known fact that diabetes is accompanied by considerable infiltration of fat in the liver, it presumably is not capable of resulting in the degree of fatty infiltration illustrated in his case. Obviously, if there was any relation whatever between the diabetes and the patient's disease, the diabetes should be secondary to pancreatic destruction. In Rosenberg's case, as in ours, a definite possible etiologic factor for the development of the pancreatic and liver disease existed; namely, cholecystitis.

In our case the pathology was confined largely to the acinar tissue of the pancreas and, estimating roughly, showed moderate to extreme changes in three-fourths of the pancreatic tissue. The islets appeared normal histologically, though perhaps decreased somewhat in number. On the whole, this case does not appear to support the suggestion of Dragstedt that lipocaic is elaborated by the alpha cells of the islets, although it would be entirely possible to have alpha cells deficient in function but showing no abnormality histologically with ordinary stains. Staining for granules in the alpha cells was not attempted because ten hours had elapsed between the time of death and the autopsy.

It is well known that fatty changes in the liver, more or less marked in degree, may arise from a variety of causes. These include toxins, both endogenous (bacterial) and exogenous (alcohol, chloroform, phosphorus), as well as anoxia (in pneumonias, etc.) which may interfere with the utilization of fats and cause their accumulation to excess in the liver. However, in the patients herein discussed, there appears to be no doubt that the fatty liver was secondary to the pancreatic lesion, particularly after consideration of the experimental data of Dragstedt and others as already discussed.

SUMMARY

During the past two or three years there have been six cases (including our own) reported having a severe grade of fatty infiltration of the liver and fibrosis of the pancreas. There is good evidence, experimental and clinical, that the lesion in the liver is secondary to pancreatic insufficiency. There can be little doubt that the pancreatic steatorrhea of infancy and childhood is the same disease as that exemplified by the six cases herein discussed. Manifestions such as diarrhea with foul bulky fatty stools, weakness, anorexia, nausea, vomiting, epigastric distress or pain and loss of weight are symptoms in common. About the only symptom not seen in each group is osteoporosis, a condition seen occasionally in children suffering from the disease; failure to encounter this in adults is easily explained on the basis of growth demands of childhood. The etiologic factors are unquestionably variable, consisting of congenital malformation of ducts, fetal pancreatitis, and vitamin deficiency in children, and pancreatic stones or gall bladder disease in adults. Whether or not an additional factor, such as a deficiency of some other glandular organ, is necessary for development of the disease cannot as yet be foretold. There is likewise a wide variation in the manifestations of the disease, but certainly no greater than is noted in many other diseases. With the amount of clinical data obtained from a study of the six cases, it now appears that an accurate diagnosis can readily be made without operation or autopsy. Unquestionably, lipocaic is very helpful in the treatment of the disease, and may even be curative so long as its administration is maintained at proper intervals.

REFERENCES

1. Fisher, N. F.: Attempts to Maintain the Life of Totally Pancreatectomized Dogs Indefinitely by Insulin, Am. J. Physiol. **67**: 634, 1924.
2. Allan, F. N., Bowie, D. J., Macleod, J. J. R., and Robinson, W. L.: Behavior of Depancreatized Dogs Kept Alive With Insulin, Brit. J. Exper. Path. **5**: 75, 1924.
3. Hershey, J. M., and Soskin, S.: Substitution of Lecithin for Raw Pancreas in the Diet of Depancreatized Dogs, Am. J. Physiol. **98**: 74, 1931.
4. Best, C. H., Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**: 94, 1933.
5. Dragstedt, L. R., Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**: 175, 1936.

6. Best, C. H., and Ridout, J. H.: The Pancreas and the Deposition of Fat in the Liver, Am. J. Physiol. **122**: 67, 1938.
7. Dragstedt, L. R.: The Present Status of Lipocaic, J. A. M. A. **114**: 29, 1940.
8. Elman, R., and McCaughan, J. M.: On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of Total Loss of Pancreatic Juice, J. Exper. Med. **45**: 561, 1927.
9. Berg, B. N., and Zucker, T. F.: Liver Changes After Deprivation of External Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **29**: 68, 1931.
10. Van Prohaska, J., Dragstedt, L. R., and Harms, H. P.: The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatectomized Dog, Am. J. Physiol. **117**: 166, 1936.
11. Andersen, Dorothy: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, Am. J. Dis. Child. **56**: 344, 1938.
12. Davie, T. B.: Massive Replacement of the Pancreas by Adipose Tissue, J. Path. & Bact. **46**: 472, 1938.
13. Harper, Margaret: Congenital Steatorrhea Due to Pancreatic Defect, Arch. Dis. Childhood **13**: 45, 1938.
14. Hess, J. H., and Saphir, Otto: Celiac Disease (Chronic Intestinal Indigestion). A Report of Three Cases With Autopsy Findings, J. Pediat. **6**: 1, 1935.
15. Snell, A. M.: Tropical and Non-Tropical Sprue (Chronic Idiopathic Steatorrhea): Their Probable Interrelationship, Ann. Int. Med. **12**: 1632, 1939.
16. Choy, P. D., and Oh, H. Y.: A Case of Pancreatic Stone, China M. J. **45**: 54, 1931.
17. Paviot, J., Plauchu, M., and Loras, O.: Pancreatitie sclerokystique, suppure chronique, accompagnee de lithiase pancreatique et de diabete. Gangrene pulmonaire terminale, Lyon méd. **155**: 509, 1935.
18. Snell, A. M., and Comfort, M. W.: Hepatic Lesions Presumably Secondary to Pancreatic Lithiasis and Atrophy, Am. J. Dig. Dis. **4**: 215, 1937.
19. Rosenberg, D. H.: A Proved Case of Recovery from Fatty Metamorphosis of the Liver After Treatment With Lipocaic, Am. J. Digest. Dis. **5**: 607, 1938.
20. Norris, E. H., Beard, A. A., and Gerber, L. S.: Atrophy of the Pancreas With Extreme Fatty Metamorphosis of the Liver and Steatorrhea, Arch. Path. **26**: 1234, 1938.
21. Chaikoff, I. L.: Survival of Two Depancreatized Dogs Treated With Insulin, Proc. Soc. Exper. Biol. & Med. **33**: 211, 1935.
22. Somogyi, M.: Blood Diastase as an Indication of Liver Function, Proc. Soc. Exper. Biol. & Med. **32**: 538, 1934; Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**: 399. 1938.
23. Foley, E. F., Keeton, R. W., and Kendrick, Darling D.: Alterations in Serum Protein as an Index of Hepatic Failure, Arch. Int. Med. **60**: 64, 1937; Alterations in Serum Proteins as an Index of Liver Failure, Proc. Soc. Exper. Biol. & Med. **33**: 430, 1935.
24. Whipple, A. O.: Pancreatic Asthenia as a Post-Operative Complication in Patients With Lesions of the Pancreas, Ann. Surg. **78**: 176, 1923.

THE LATE PHASE OF CONGESTIVE SPLENOMEGALY (BANTI'S SYNDROME) WITH HEMATEMESIS BUT WITHOUT CIRRHOSIS OF THE LIVER

Further Observations on the Etiology of Banti's Syndrome and the Effect on Prognosis of Certain Variations in the Portal Venous Pattern

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THE early descriptions of Banti[1, 2] and his concept of the etiology and clinical course of so-called Banti's disease are so entrenched in medical literature and text that it becomes difficult to alter that which so long has received the sanction of common usage. The following quotation from Cecil[3] epitomizes the generally accepted textbook version of the disease: "Splenic anemia (Banti's disease) is a chronic disease of unknown origin, probably toxic, and primary in the spleen, and is characterized by splenomegaly, anemia, and leukopenia, a tendency to gastric hemorrhage, increased formation and destruction of blood cells, and later by cirrhotic changes in the liver, with ascites and jaundice."

The clinical sequence as described by Banti of (1) primary splenomegaly, toxic in origin, (2) an intermediate stage, and (3) finally, the third stage with cirrhosis of the liver, of course, has often been disputed. The German concept of *Stauungsmilz*[4] was an early attempt to controvert Banti's theory. This in general precludes the possibility of a toxic substance producing primary splenic enlargement and predicates the existence of chronic portal stasis as a precursor of the splenomegaly. It is surprising to find how little convincing evidence has been presented to prove either of the two aforementioned contentions.

The Spleen Clinic of the Presbyterian Hospital has presented a series of papers[5-7] in recent years supporting the view that the picture presented by Banti is confusing and misleading in respect to etiology, clinical course, and treatment. Our group is firmly convinced that the etiology of Banti's syndrome may be entirely explained on a mechanical basis; i.e., portal bed obstruction with an associated "portal hypertension."[8] The site of the obstructive factor causing the portal hypertension and splenomegaly may be intra- or extrahepatic. The term "congestive splenomegaly" suggested by Larrabee,[9] we believe, is more descriptive than Banti's disease or Banti's syndrome.

The usual intrahepatic lesion producing congestive splenomegaly is, of course, cirrhosis of the liver. This paper, however, is solely con-

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cerned with a selected group of 15 patients, all presenting the typical symptoms, signs, and blood studies usually associated with this syndrome. Severe gastrointestinal bleeding occurred in each of these patients, yet in no case was there coexistent liver cirrhosis. We shall demonstrate that in most of these patients an extrahepatic obstructive factor was present in the portal venous bed. In every instance in which splenic vein pressures were taken at operation, a "portal hypertension" could be determined. The nonexistence of liver cirrhosis in all was established by most of the available methods at our command. These procedures include various liver function tests carried out before operation, gross examination of the liver at operation, and liver biopsy on one or more occasions in the same patient. Furthermore, evidence will be advanced to show that cirrhosis not only was absent at the time of operation, but did not develop as established by the subsequent clinical course and further laboratory studies for varying periods up to nineteen years after operation. In four instances this lack of liver disease has had additional confirmation by autopsy as well.

EVIDENCE DEMONSTRATING THE ABSENCE OF LIVER CIRRHOSIS IN THIS GROUP OF CASES

Table I will clarify the statements as to the nonexistence of liver cirrhosis in all these cases. In the first 2 patients operated upon in 1920 and 1922, there is the least evidence. In each instance there is only the surgeon's operative description of a normal liver. However, in each of the succeeding 13 patients, almost all of whom were operated upon by Allen O. Whipple or myself, at least two forms of corroborative evidence are presented. Histologic proof of normal liver tissue was available in 10 of the 15 cases. Liver biopsy was done at operation in 7 instances and 1 of these also had subsequent autopsy confirmation. Autopsy was also obtained in 3 additional patients who had no liver biopsy at the time of operation.

It is our experience that the bromsulphthalein test is a reliable index of hepatic damage. We have felt particularly secure in our interpretation of these tests because in every case no retention or only a slight trace of the dye was present in the blood after thirty minutes and no equivocal or border line determinations occurred. Bauman and Orr's[10] recent report on the accuracy of the bromsulphthalein test is of interest In not one instance in our series was there any inconsistency between liver function test, liver biopsy, or necropsy findings.

NATURE OF THE EXTRAHEPATIC LESIONS

As designated in Table I an extrahepatic obstructive factor was demonstrable in the portal venous system of 8 of the 15 patients examined (Cases 4, 5, 6, 7, 9, 11, 12, and 14). This was recognized at the operating table in 4 instances and 4 times it was only demonstrable at autopsy. The failure to discover an obstructive factor in the other 7 cases is not

TABLE I

EVIDENCE OF NONEXISTENCE OF LIVER CIRRHOSIS

CASE NO.	LIVER FUNCTION STUDIES BEFORE OPERATION	OPERATIONS*	OPERATIVE GROSS APPEARANCE OF LIVER OBSTRUCTIVE FACTORS	FINDINGS			
				MICROSCOPIC DIAGNOSIS OF LIVER BIOPSY	VENOUS PRESSURE	LIVER FUNCTION STUDIES AFTER OPERATION	AUTOPSY FINDINGS LIVER OBSTRUCTIVE FACTOR
1	----------	S	Normal Undetermined	No biopsy	----------	----------	----------
2	----------	E	Normal Undetermined	No biopsy	----------	----------	----------
3	----------	S	Normal Undetermined	No biopsy	----------	13 yr. postoperatively bromsulphthalein test normal Ser. prot. 7.2% Ser. alb. 4.3 Ser. glob. 2.9	----------
4	----------	S	Normal Undetermined	No biopsy	----------	12 yr. postoperatively bromsulphthalein test normal Ser. prot. 6.4% Ser. alb. 4.0 Ser. glob. 2.4	Normal liver Stenosis of portal vein just below liver
5	----------	S	Normal Thrombosis of splenic vein	No biopsy	----------	----------	----------
6	----------	S	Normal Undetermined	No biopsy	----------	----------	Normal liver Cavernomatous transformation of portal vein
7	Bromsulphthalein test normal Ser. prot. 5.5% Ser. alb. 3.6 Ser. glob. 1.9	S	Normal Undetermined	Biopsy: normal liver	----------	----------	Normal liver Cavernomatous transformation of splenic and portal veins
8	Bromsulphthalein test normal Ser. prot. 5.9% Ser. alb. 4.2 Ser. glob. 1.7	S	Normal Undetermined	Biopsy: normal liver	Splenic V.—370 mm. Arm V.—50 mm.	----------	----------

9	----------	S	Normal Thrombosis of splenic vein	Biopsy: normal liver	----------	2 yr. postoperatively bromsulphthalein test normal Ser. prot. 8.3% Ser. alb. 4.9 Ser. glob. 3.4	----------
10	----------	S L	Normal Undetermined	Biopsy: normal liver	----------	3 yr. postoperatively bromsulphthalein test normal Ser. prot. 6.2% Ser. alb. 4.2 Ser. glob. 2.0	----------
11	Bromsulphthalein test normal Ser. prot. 7.1% Ser. alb. 4.2 Ser. glob. 2.9	S	Normal Thrombosis of junction of splenic and portal veins	Biopsy: normal liver	Splenic V.—400 mm. Arm V.—170 mm.	----------	----------
12	----------	S	Not noted Undetermined	No biopsy	----------	----------	1 right lobe, no cirrhosis, focal necrosis present; left lobe represented by small nubbin of tissue Stenosis of lower end of portal, above splenic vein
13	Bromsulphthalein test normal Ser. prot. 7.7% Ser. alb. 4.4 Ser. glob. 3.3	S	Normal Undetermined	Biopsy: normal liver	Splenic V. 330 mm. Arm V. 55 mm.	----------	----------
14	----------	L	Not noted Thrombosis of splenic vein	No biopsy	----------	6 yr. postoperatively galactose tolerance test normal Ser. prot. 8.03% Ser. alb. 5.09 Ser. glob. 2.94	----------
15	Ser. prot. 6.9% Ser. alb. 4.3 Ser. glob. 2.6	S	Normal Undetermined	Biopsy: normal liver	Splenic V. 465 mm. Arm V. 110 mm.	----------	----------

*S, Splenectomy; L, ligation of splenic vessels; E, exploratory celiotomy.

necessarily a weakness in our hypothesis but is due rather to the technical difficulties involved in an operative examination of the portal venous bed away from splenic hilum, particularly behind the head of the pancreas.

In this connection it is of interest to note that one patient (Case 4), although reported in two previous papers in 1936 and again in 1939 as having an "obstructive factor" undetermined, has recently died, and a post-mortem examination was made. This patient had had a splenectomy at 5 years of age and was subsequently followed for thirteen years. During this period he continued to have recurring hematemeses and melena and was admitted to the Presbyterian Hospital twenty-four times. Bleeding was always severe and occurred approximately twenty-one times via the esophageal route and ten times per rectum. Because of (1) the normal appearing liver at operation, (2) the normal blood count between bleeding episodes, (3) normal liver function tests at the ninth, eleventh, and twelfth years after splenectomy, we felt secure in our belief that cirrhosis never did exist and that it subsequently had not developed. This patient finally died only seven months ago. Before section was started, one of our staff, William P. Thompson, predicted the finding of a normal liver and also an obstructive lesion in the portal vein close to liver. Both predictions were confirmed.

The nature of the extrahepatic lesions responsible for obstruction to splenic blood in this series are listed as follows:

1. Thrombosis of splenic vein (traumatic)	Case 5
2. Thrombosis of splenic at junction with portal vein (traumatic)	Case 11
3. Thrombosis of splenic vein (nontraumatic)	Case 9
4. Thrombosis of splenic vein (nontraumatic)	Case 14
5. Stenosis of portal vein (upper end) just below liver	Case 4
6. Stenosis of portal vein (lower end) above entrance of splenic vein	Case 12
7. Cavernomatous transformation of portal vein	Case 6
8. Cavernomatous transformation of junction of portal vein and splenic veins	Case 7

The extrahepatic obstructive lesions just detailed occurred in the respective sites indicated on Fig. 1.

THE ANATOMICAL PORTAL VENOUS PATTERN AS A DETERMINANT OF SYMPTOMATOLOGY AND PROGNOSIS

In an analysis of the long-term results following splenectomy in this entire group, one rather interesting observation has become apparent. From an examination of Fig. 2 it will be seen that 9 of these patients continued to have intestinal bleeding following operation for periods varying from eight months to thirteen years; whereas, 6 were immediately relieved of this serious complication and have remained so for long periods of time, in Case 1 for as long as nineteen years. Why should such a marked variation in clinical behavior occur? This phase

of the problem has been given a good deal of thought and it is our belief that we may have the answer. It is our purpose to demonstrate that (1) the site of the obstruction and (2) variations in the anatomical distribution of the veins forming the portal system may be the determining factors governing symptomatology, course, and eventual prognosis in any individual case. Referring again to Fig. 1, it seems obvious that a lesion occluding the portal vein close to the liver will impede the flow of a much greater volume of blood than a similar stenotic process located in the splenic vein close to the hilum of the spleen.

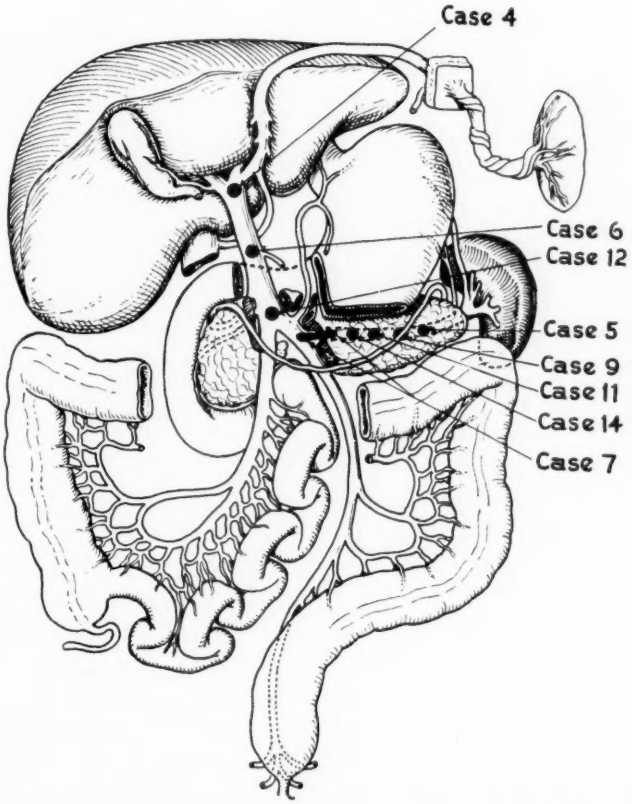

Fig. 1.—Schematic drawing (after F. Paitre, H. Lacaze, S. Dupret), indicating the sites of the obstructive factor in the cases designated.

The former involves the entire return flow of the portal system; whereas, the latter affects only the splenic fraction, or approximately 20 per cent. This question of the site of the obstruction is further qualified, we believe, by the second consideration just alluded to. This second consideration is the variations that occur in the anatomy of the veins forming the portal system.

Fig. 3 portrays six different anatomical patterns taken from six standard sources. Even cursory inspection of these figures will show that an obstructive lesion as indicated in *B* will produce much more profound alterations in intestinal physiology than the identical lesion

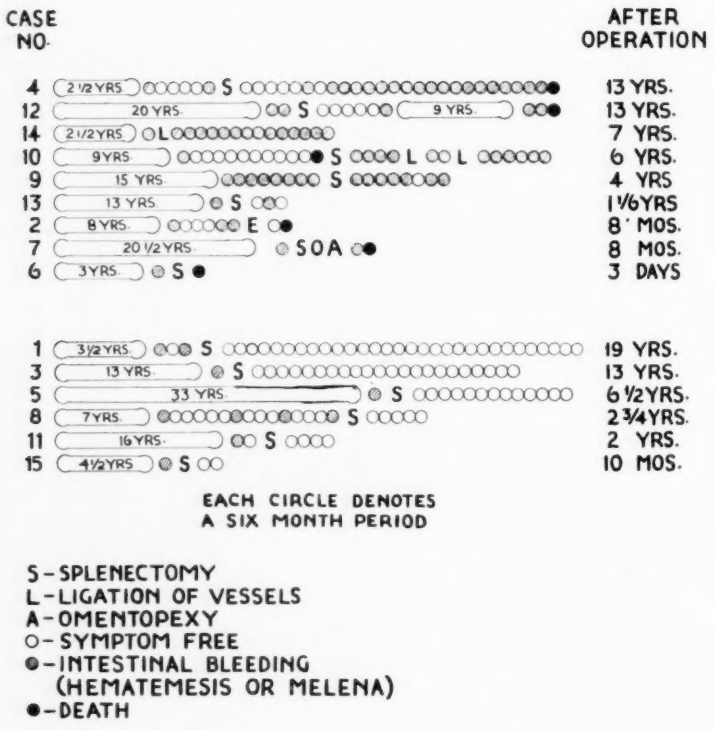
CASE NO.
AFTER OPERATION
4 2 1/2 YRS. S 13 YRS.
12 20 YRS. S 9 YRS. 13 YRS.
14 2 1/2 YRS. L 7 YRS.
10 9 YRS. S L L 6 YRS.
9 15 YRS. S 4 YRS
13 13 YRS. S 1 1/6 YRS
2 8 YRS. E 8 MOS.
7 20 1/2 YRS. S O A 8 MOS.
6 3 YRS. S 3 DAYS
1 3 1/2 YRS. S 19 YRS.
3 13 YRS. S 13 YRS.
5 33 YRS. S 6 1/2 YRS.
8 7 YRS. S 2 3/4 YRS.
11 16 YRS. S 2 YRS.
15 4 1/2 YRS. S 10 MOS.
EACH CIRCLE DENOTES A SIX MONTH PERIOD
S - SPLENECTOMY
L - LIGATION OF VESSELS
A - OMENTOPEXY
○ - SYMPTOM FREE
◉ - INTESTINAL BLEEDING (HEMATEMESIS OR MELENA)
● - DEATH

Fig. 2.

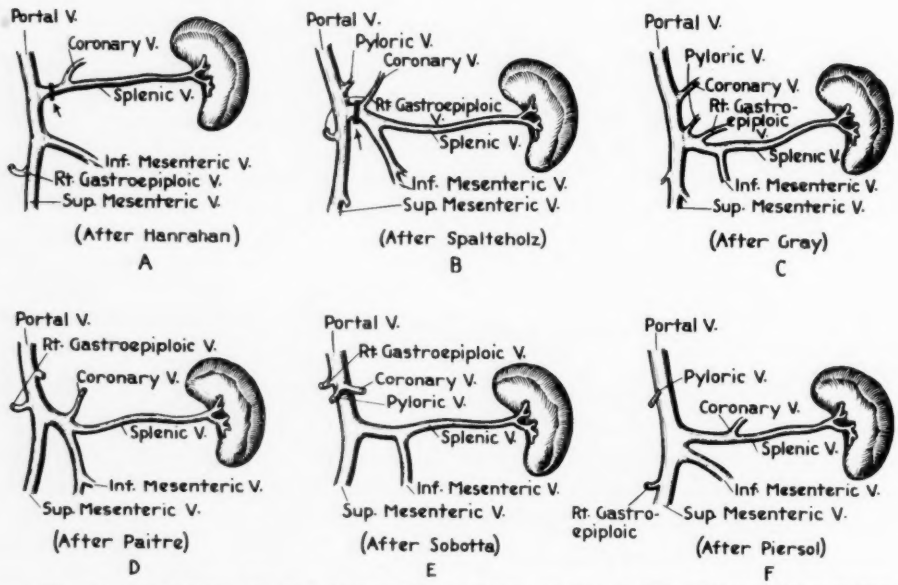

Fig. 3.—Variations in the anatomical pattern of the portal system illustrating how an obstructive factor of the same site in different individuals may result in marked differences in clinical behavior.

occurring in an individual possessed of a portal system as illustrated in *A*. Additional observations along these lines will explain many of the vagaries and alterations in clinical behavior in these patients. To quote specific examples from our series:

Case 4 showed a stenotic lesion of portal vein immediately subjacent to liver, and Case 12 lower down in the portal vein. Regardless of the venous pattern in such a situation the entire portal flow is impeded. Splenectomy, although returning the blood picture to normal, will only remove a small burden of the already overloaded collateral circuit. Intestinal bleeding in this type of case, of course, will continue and will not only evolve from esophageal varices but also from small and large bowel. The latter is due to blockage of the superior and inferior mesenteric venous outflow. These are the cases in which melena will always be a dominant feature.

In Cases 5 and 11, however, the obstructive factor was a thrombosis of the splenic vein. This involved only the splenic contribution to the portal flow. Establishment of a collateral circulation via the vasa brevia resulted in bleeding esophageal varices. Following splenectomy, this recurring thrust on the varices was removed. These patients had subsequently no further bleeding. Between these two extremes all gradations in clinical behavior are possible and are dependent, as mentioned before, on (1) the site of the obstruction and (2) the disposition of the accessory veins supplying the portal vein.

SUMMARY

A group of fifteen cases is presented, all with the characteristic features of Banti's syndrome and all with gastrointestinal bleeding as a dominant symptom. Although exhibiting the presumably late symptom of hematemesis, none of these cases had cirrhosis of the liver at operation or subsequently for long periods of time up to nineteen years after operation. The etiology of the splenomegaly can be entirely explained on a mechanical basis with a primary obstructive factor in the portal bed and an associated portal hypertension. The evidence presented therefore contradicts the sequence described by Banti of a primary splenomegaly and a subsequent cirrhosis due to a hypothetical toxic agent.

A variety of extrahepatic lesions have been listed, all capable of producing venous stasis. In the four instances in which splenic vein pressures were determined a definite venous hypertension was recorded. This confirms similar observations previously reported by this clinic in other forms of Banti's syndrome.

The frequency of anomalies in the portal system is stressed.

In this group of cases of congestive splenomegaly due to extrahepatic obstructive lesions, the prognosis and variations in clinical behavior

are dependent on two factors: (1) the site of the obstructive lesion and (2) variants in the anatomy of the venous pattern. To the best of our knowledge, this latter concept is herein presented for the first time.

REFERENCES

1. Banti, Guido: Splenomegalie mit Levercirrhose, Beitr. z. path Anat. **24**: 21, 1898.
2. Banti, Guido: Ueber Morbus Banti, Folia haemat. **10**: 33, 1910.
3. Cecil, R. L.: A Text Book of Medicine, Philadelphia, 1937, W. B. Saunders Co.
4. Eppinger, H.: Die Stauungsmilz beim Menschen: Die Hepatolienalen. Erkrankungen, Berlin, 1920, Julius Springer, pp. 384-493.
5. Rousselot, L. M.: The Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome. J. A. M. A. **107**: 1788, 1936.
6. Rousselot, L. M.: Congestive Splenomegaly (Banti's Syndrome), Bull. New York Acad. Med. **15**: 188, 1939.
7. Rousselot, L. M., and Thompson, W. P.: Experimental Production of Congestive Splenomegaly, Proc. Soc. Exper. Biol. & Med. **4**: 705, 1939.
8. Thompson, W. P., Caughey, J. L., Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), J. Clin. Investigation **16**: 571, 1937.
9. Larrabee, R. C.: Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, Am. J. M. Sc. **188**: 745, 1934.
10. Bauman, L., and Orr, L.: Bromsulphalein Test, New York State J. Med. **38**: 17, 1938.
11. Hanrahan, E. M., and Vincent, B.: Surgery of the Spleen, Lewis' Practice of Surgery VI, Hagerstown, Md., 1939, W. F. Prior Co., Chap. XV, p. 74.
12. Spalteholz, W.: Hand Atlas of Human Anatomy, ed. 7, Philadelphia, J. B. Lippincott Co., vol. II, p. 477.
13. Gray, H.: Anatomy of the Human Body, ed. 23, Philadelphia, 1936, Lea and Febiger, p. 675.
14. Paitre, F., Lacaze, H., and Dupret, S.: Pratique Anatoma-Chirurgicale Illustrée, Paris, 1934, G. Doin et Cie, vol. I, p. 277.
15. Sobotta, J.: Human Anatomy, ed. 4, New York, 1936, G. E. Stechert and Co., vol. III, p. 89.
16. Piersol: Human Anatomy, ed. 9, Philadelphia, 1930, J. B. Lippincott Co., p. 919.

THE PROPHYLACTIC USE OF SULFANILAMIDE IN ABDOMINAL SURGERY

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IN VIEW of the dramatically successful results of chemotherapy in such diverse infections as hemolytic streptococcic peritonitis, cellulitis, and septicemia, colon bacillus pyuria, gonococcic urethritis, and pneumococcic pneumonia, the question has logically arisen as to the possible effectiveness of sulfanilamide or one of its derivatives in peritonitis of intestinal origin. The literature on the surgery of the colon has been concerned to a large extent with measures designed to minimize the threat of peritonitis as a complication of such operations. That peritonitis continues to occupy the major position among the causes of death following surgical procedures on the large intestine is shown in Table I. The operative mortality of radical procedures averages about 18 per cent and about 40 per cent of the deaths are due to peritonitis. The data of Rankin[7] show that, while the mortality following simple colostomy may be very low, almost 60 per cent of the deaths that do occur are attributable to peritonitis. If sulfanilamide can be safely employed to reduce the incidence of postoperative peritonitis, a major advance will have been achieved.

In a previous publication,[9] dealing with the use of sulfanilamide in hemolytic streptococcic infections, expression was given to the opinion that the effectiveness of sulfanilamide in any lesion is conditioned more by the pathologic character of the infectious process than by the degree of susceptibility of the infecting organisms. As a result of a three-year experience in the use of sulfanilamide in the prevention and treatment of peritonitis on our surgical service at the Hospital of the University of Pennsylvania, we are inclined to reaffirm this opinion. In this paper we will undertake to supply a rational basis for sulfanilamide therapy in polymicrobic peritonitis and to present a summary of our experience to date.

BACTERIOLOGIC CONSIDERATIONS IN PERITONITIS OF INTESTINAL ORIGIN

Peritonitis of intestinal origin is usually a mixed bacterial infection in which the organisms most frequently found are the *Bacillus coli,* the green or nonhemolytic streptococci, and the Welch bacillus. The careful studies of Meleney, Harvey, and Zaytseff-Jern[10] on the bacterial flora of peritonitis, in which sound bacteriologic methods were used, showed

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B. coli in 87 per cent, hemolytic and nonhemolytic streptococci in 7 per cent and 21 per cent respectively, green streptococci in 49 per cent, and *Clostridium welchii* in 38 per cent. The disease was more severe and the mortality higher when more than one type of organism was present. That the interplay of synergisms among these bacteria was an important factor in the pathogenesis of peritonitis was further emphasized by the experimental studies of Meleney, Olpp, Harvey, and Zaytseff-Jern.[11] In their experiments mice succumbed when small fractions of the lethal doses of individual strains of *B. coli*, streptococci, and *Cl. welchii* were mixed prior to intraperitoneal inoculation. These organisms as they exist in feces are probably saprophytic rather than parasitic, deriving their essential nutrition from the fecal contents rather than from the host tissues. Before they can shift from the saprophytic phase to the parasitic or invasive phase, the ground usually has been prepared by primary injury or loss of blood supply in some area of the bowel. The proteolysis of tissue which takes place in such an injured area provides the bacteria with an environment in the tissues themselves which is suited to their needs, and invasion of the bowel wall and later of the peritoneum itself may occur. In postoperative peritonitis necrosis of tissue at the suture line or leakage of fecal contents into the peritoneal cavity is the most frequent initiating factor. After the adaptation of intestinal bacteria to the parasitic state has been achieved, they may then continue to multiply in tissues wherein primary necrosis has not occurred. The form of peritonitis most frequently encountered, of course, is that resulting from appendicitis. In this type of peritonitis the bacteria have successfully bridged the existing gap between the saprophytic state of intestinal bacteria and the parasitic state of bacteria involved in an invasive lesion, the necrosis of the appendix itself being the most important factor involved in this change. A peritoneal defense quite adequate to deal with avirulent saprophytes may be quite overwhelmed if these same organisms have become toxin-producing parasites by multiplying in necrotic tissue. We wish merely to re-emphasize the well-known fact that whether or not peritonitis results from fecal contamination incident to a colon anastomosis probably depends as much on the amount of necrosis at the suture line as on any other consideration. It may be assumed that spreading peritonitis will not develop unless the contaminating bacteria encounter in the bowel wall or peritoneum an environment capable of supplying to them the nutritive materials required for their multiplication and toxin production.

METHODS OF REDUCING INCIDENCE AND MORTALITY OF PERITONITIS

The risk of postoperative peritonitis in surgery has probably been substantially lowered by the institution of a number of improvements in surgical technique and management. Among these improvements the most important are: (1) atraumatic methods of anastomosis and the use of silk for seroserous sutures; (2) preliminary enterostomy with

preoperative decompression and cleansing of the bowel; (3) intubation with the Miller-Abbott double lumen tube to minimize tension proximal to the suture line; and (4) mobilization of the peritoneal defense prior to a radical operation.

It has been suggested that a factor in the lower mortality of multiple-stage procedures might be the "vaccination" of the peritoneum incident to the first stage. The recent studies of Coller and his associates[12] on dogs showed that the peritoneum was somewhat more resistant to infection by large doses of *B. coli* two weeks after a precolostomy had been performed than the peritoneum of normal dogs or of dogs four weeks after such an operation. The magnitude of the protection was not as great as that provided by the intraperitoneal injection of coli-bactragen (Steinberg)* forty-eight hours before infection.

There is little unanimity of opinion as to the value of intraperitoneal injection of substances such as coli-bactragen designed to mobilize the cellular defense of the peritoneum preoperatively. The experimental studies of Gay[13] and of Steinberg[14] have emphasized the importance of the large macrophages and the polymorphonuclear cells in the protection of serous membranes against invasive infection. These cells accumulate rapidly following the injection of sterile irritants. Since phagocytosis is presumably the chief defense mechanism of the peritoneum, there is theoretical support for the desirability of increasing the numbers of available phagocytes. Furthermore, it may be that a more rapid sealing of serosal surfaces of an anastomosis would take place if the peritoneum were mildly irritated and hyperemic. Dixon,[15] of the Mayo Clinic, is one of the strong advocates of peritoneal protection. He has reported a mortality of 6 per cent in 180 resections in vaccinated patients, as against 17 per cent in a "similar series" of unvaccinated cases. Rankin, who formerly advocated vaccination on the strength of an improved mortality record during a period in which it was used, now attributes the good results to the more careful preoperative decompression which was instituted at the same time. He has recently reported[16] 130 cases in which no vaccine was used with an 8.4 per cent mortality. Coller and Rife[17] and Ochsner and DeBakey[8] believe that the vaccine should be introduced at the time of operation only in those cases where soiling has occurred during resection and anastomosis. They believe this to be preferable to preoperative vaccination. In our experience the pain incident to the preoperative vaccination has appeared to constitute a real disadvantage. We have not employed this procedure in the cases included in this report.

SULFANILAMIDE IN PERITONITIS

It is now generally agreed that sulfanilamide owes its effectiveness in infections to its capacity to limit the multiplication of bacteria, although

*Coli-bactragen is a mixture of killed colon bacilli, aleuronat, and tragacanth.

there is considerable disagreement as to the precise mechanism by which bacteriostasis is induced. Many factors operate to influence the magnitude of the sulfanilamide effect, among them the most important being: (1) the size of the inoculum; (2) the concentration of the drug; (3) the presence or absence of leucocytes; (4) the chemical state of the medium, with particular respect to its content of split products of protein; and (5) the susceptibility of the organisms, varying almost as much among strains as among species. While the influence of these modifying factors is most clearly brought out in in vitro experiments, there is reason to believe that similar modifying influences usually obtain in vivo.

In the type of peritonitis which follows operations on the large bowel most of these factors are adjusted in such a way as to allow a drug effect of considerable magnitude. The size of the bacterial inoculum is relatively small, many of the organisms even in feces being dead or devitalized; a satisfactory concentration of drug in the peritoneal fluid may be rapidly obtained with parenteral or oral administration of the drug;[18] leucocytes are present in abundance, particularly if peritoneal protection has been instituted; and, unless a considerable amount of devitalized tissue has been left at the site of the anastomosis, there would be a minimal amount of protein-split products in the peritoneal fluid. Few data are available with respect to the susceptibility to sulfanilamide of the bacteria usually encountered in this form of peritonitis. The colon bacillus is highly susceptible to the concentrations of the drug which occur in the urine, and, in vitro, the drug has a definite effect on this organism in urine when the concentration is only 10 mg. per cent, provided protein-split products are excluded.[19] On the other hand, the nonhemolytic streptococci as a group are comparatively resistant to sulfanilamide bacteriostasis. The *Streptococcus fecalis* (Lancefield Group D) infections of the urinary tract do not respond as favorably to sulfanilamide as do most other types. Perhaps the major question involved in the successful application of sulfanilamide therapy to the mixed infections of the peritoneum is whether relative insusceptibility of the bacteria to the drug may be compensated for by a coincidence, on the favorable side, of all of the other factors tending to modify the drug effect. For example, the staphylococcus is ordinarily quite resistant to sulfanilamide in soft-tissue infections, but in the urinary tract, or in human serum with a small inoculum of staphylococci, high degrees of bacteriostasis may be demonstrated provided the concentration of drug is high and protein-split products are excluded.[19]

We are now engaged in an experimental study of the protective value of sulfanilamide in experimental infections of mice with mixtures of the ordinary intestinal bacteria. The experimental details will be presented in a later publication.

TABLE I

INCIDENCE OF PERITONITIS AS A CAUSE OF DEATH IN MORTALITY FOLLOWING OPERATIONS FOR LARGE BOWEL CARCINOMA

AUTHOR	NO. OF CASES	LOCATION	TYPE OF OPERATION	MORTALITY		DUE TO PERITONITIS
				CASES	%	%
Wilkie[1]	101	Colon	Anastomosis or Mikulicz	15	14.8	13.3
Patterson and Webb[2]	63*	Colon	Mikulicz	12	19.0	16.7
Stone and McLanahan[3]	166	Colon and rectum	Anastomosis or abdominal perineal	23	13.8	47.8
Mayo and Simpson[4]	204	Transverse	Mikulicz, anastomosis, or palliative	33	16.1	63.6
Allen[5]	653	Colon and rectum	Anastomosis, Mikulicz, or abdominal perineal	110	16.8	30.0
MacFee[6]	156	Colon	Anastomosis or Mikulicz	34	21.8	55.8
Rankin[7]	969	Colon and rectum	Colostomy	42	4.3	57.1
Ochsner and DeBakey[8]	Collected series	Colon	Anastomosis or Mikulicz	412		41.7

*Excluding 7 unfavorable cases.

Accounts of the experience gained from the use of sulfanilamide therapy in the treatment of local and diffuse peritonitis of appendical origin have been published by Corry, Brewer, and Nicol[22] and by Ravdin, Rhoads, and Lockwood.[18] The mortality of acute appendicitis in these two series before and since the institution of sulfanilamide (for the severe cases) is shown in Table II. It is recognized that

TABLE II

THE MORTALITY FROM ACUTE APPENDICITIS AND ITS COMPLICATIONS

	TOTAL CASES	DEATHS	DRAINED (%)	GROSS MORTALITY (%)
Service E—Hospital of the University of Pennsylvania:				
Before the use of sulfanilamide (to 1936)	552	8*	37.0	1.4
With the use of sulfanilamide in cases showing infection outside the appendix (1936 to 1940)	318	1†	41.0	0.3
Total	870	9	38.0	1.0
Corry, Brewer, and Nicol: Brit. M. J. **2**: *561, 1939:*				
Before the use of sulfanilamide (1934-1938)	1,131	60		5.3
With the use of sulfanilamide in cases of peritonitis (1938-1939)	273	3‡		1.1
Total	1,404	63		4.5

*One death occurred in a patient not operated upon.

†This patient did not receive sulfanilamide until two days after operation.

‡Twenty-six patients with "general peritonitis" (including all 3 deaths) and 15 with "abscess" and removal of appendix were treated with sulfanilamide and its derivatives.

one is justified in reserving judgment as to the statistical significance of these figures. However, it may be pointed out that the only death in our treated group was a patient who did not have peritonitis at the time of operation and who died as a result of separation of the stump ligature and massive soiling of the peritoneum. Sulfanilamide was not started until the third day after operation, when widespread infection was present. It was on the basis of our conviction that sulfanilamide had been a factor in saving the lives of a few desperately sick patients in this group that we were encouraged to make a trial of the drug in the prevention and treatment of other types of peritonitis. It appeared that sulfanilamide should be even more effective in preventing postoperative peritonitis than in treating the established disease. In appendical peritonitis all of the above-mentioned factors influencing the magnitude of the sulfanilamide effect except that of drug concentration may be unfavorably adjusted; even though the necrotic appendix may be removed, it is impossible always to evacuate necrotic exudate on the peritoneal surfaces and the leucocytic exudate at the time of operation may be already overwhelmed by the number of actively multiplying bacteria (Steinberg's tertiary stage[23]).

During 1938 we started using sulfanilamide in the treatment of inflammatory and traumatic bowel perforations. We and our associates were so impressed with the recovery of some of these cases that we started using prophylactic sulfanilamide in all of our bowel resections. The volume of material does not warrant our presenting it as a statistical study. Instead, we have elected to include in the three accompanying tables all of the cases of these types in which sulfanilamide has been used. Tables III and IV present a consecutive series of 22 colon resections of various types, 16 in cases of carcinoma and 6 in nonmalignant lesions. The type of operation performed in each case varied with the location and extent of the lesion and the condition of the patient. Ileocolostomy, employing open technique, was used in 6 instances. In all of the other cases the involved bowel was removed and one or both ends of the resected intestine were brought out through the abdominal wall as a terminal or a double-barrel colostomy. In one case (No. 40929) the tumor had invaded the jejunum, necessitating resection of a segment of jejunum. The continuity of the small intestine was restored by side-to-side anastomosis. In Case 41646 the tumor had perforated and a small abscess was opened during the process of removing the mass. In Case 43211 resection was carried out for a lesion of the cecum which proved pathologically to be an acute diverticulitis. Spiking temperature, chills, and jaundice appeared on the fifth day, two days after stopping sulfanilamide. Although the blood culture was negative, the existence of suppurative pylephlebitis seemed probable. Rapid improvement occurred after drug administration was resumed. Ottenberg and Berck[25] have al-

ready reported the recovery under sulfanilamide treatment of two cases of suppurative pylephlebitis.

There were no deaths from peritonitis in the group of twenty-two resections and in no case was there clinical evidence of peritonitis during the postoperative course. The one death which occurred (Case 43236) was due to coronary occlusion on the first postoperative day. This series is small and of doubtful statistical significance. However, in view of the usual incidence of peritonitis as a cause of death in bowel resection, as shown in Table I, we have naturally been encouraged by the results of prophylactic sulfanilamide therapy during this first year of its trial. Our impression of the probable value of the drug in these cases is fortified through our previously cited experience in the treatment of peritonitis following appendicitis.

The toxic drug reactions which occurred in three cases were mild in character and responded to stopping the treatment.

Infection of the abdominal wound occurred in four cases. It is possible that these wound infections might have been prevented if treatment had been continued for longer periods of time. The cellular defenses of the peritoneum rapidly may complete the destruction of contaminating bacteria which are inhibited by sulfanilamide. Bacteria in an abdominal wound, however, are protected against the maximal drug effect by the presence of products of tissue proteolysis and may grow out and cause infection if chemotherapy is continued for only a brief period.[9, 10]

Table V presents 6 instances of inflammatory and traumatic perforation of the intestinal tract in which sulfanilamide treatment was used. The recovery of the two patients with local peritonitis associated with sigmoid diverticulitis is perhaps not at all remarkable, but they are included in the interest of keeping the series complete. In the other 4 cases the nature of the lesions found at operation and the immediate condition of the individual patients was such as to lead us to believe that the prognosis was extremely grave. Case 42924, a 70-year-old man with widespread peritonitis from a ruptured diverticulitis of the right colon, lived long enough to develop a localized pelvic abscess, which was drained, but he died three weeks following the initial operation, from myocardial failure.

Surgeons have been hesitant to employ sulfanilamide and its derivatives in the prevention and treatment of peritonitis of intestinal origin. This has been due to a well-entrenched belief that sulfanilamide is effective only in infections due to certain cocci, particularly the hemolytic streptococcus. It is our impression that under special experimental or pathologic conditions which favor drug action, sulfanilamide may have some degree of antibacterial effect against almost all species of pathogenic bacteria and that the pathologic character of the lesion is of greater importance in conditioning the magnitude of the drug effect

TABLE

PROPHYLACTIC SULFANILAMIDE

HOSPITAL NO.	AGE	ADMISSION DATE	DATE OF DISCHARGE	DIAGNOSIS	OPERATION	
					DATE	TYPE
43252	65	10/24/39	11/26/39	Carcinoma of cecum with metastasis to liver	11/11/39	Ileocolostomy
42654	63	7/10/39	8/10/39	Carcinoma of cecum	7/11/39	Ileocolostomy; resection of cecum and right colon, one stage
43464	70	11/22/39	1/24/40	Carcinoma of cecum	11/25/39	Lahey-Bloch-Mikulicz resection
41125	49	1/24/39	2/15/39	Carcinoma of ascending colon	1/31/39	One-stage ileocolostomy and resection
43236	65	10/31/39	11/ 5/39	Carcinoma of ascending colon	11/ 4/39	Lahey-Bloch-Mikulicz resection
40232	56	10/ 1/38	10/22/38	Carcinoma of ascending colon	10/ 6/39	Ileocolostomy (first stage of resection)
42139	52	5/29/39	7/ 5/39	Carcinoma of hepatic flexure	6/ 1/39	Mikulicz resection
40929	51	1/30/39	3/22/39	Carcinoma of transverse colon with involvement of jejunum	1/31/39	Cecostomy
					2/23/39	Resection of colon and jejunum (Devine)
22671	67	6/14/39	7/ 5/39	Carcinoma of descending colon	6/17/39	Obstruction resection (Rankin)
37419	68	3/13/39	4/ 8/39	Carcinoma of sigmoid	3/23/39	Resection and colostomy, first stage
44202	51	12/18/39	1/21/40	Carcinoma of sigmoid	12/21/39	Obstruction resection (Rankin)
43004	47	9/11/39	10/ 2/39	Carcinoma of sigmoid involving uterus	9/12/39	Mikulicz resection; partial hysterectomy
41646	53	4/ 8/39	5/ 1/39	Carcinoma of sigmoid	4/ 8/39	Resection and colostomy, first stage; lesion perforated
41977	71	5/10/39	6/20/39	Carcinoma of rectum	5/13/39	Lockhart-Mummery; peritoneum opened
40935	51	1/ 2/39	2/14/39	Carcinoma of rectosigmoid	1/ 7/39	First stage abdominal perineal
41515	60	3/15/39	4/18/39	Carcinoma of rectum	3/21/39	Colostomy
					4/ 1/39	Perineal excision

*h, Hypodermoclysis; p.o., by mouth.

III

IN COLON RESECTIONS

SULFANILAMIDE		DAYS OF DRUG	COMPLICATIONS	COURSE	REMARKS
PRE-OPERATIVE (GM.)	POST-OPERATIVE (GM.)*				
4.0	16.0 h.	4	Hematoma of wound	Very smooth; out of bed ninth day	
3.2	9.6 h. 4.0 p.o.	4	Chill with temperature to 104° fourth day; wound infection	Smooth except for wound infection	
4.0	16.0 h.	5		Smooth	
4.0	19.2 h.	4	None	Normal T.P.R. after fifth day; smooth	
6.5	6.4 h.	1	Coronary occlusion		Died
	9.6 h. 24.0 p.o.	8	None	Very smooth; highest temperature 100.6°	
4.0	None	–	None	Smooth; temperature normal after ninth day	
	14.4 h.	4	None	Smooth	
1.5	29.1 h.	5	None	Highest temperature 100.4° on second day	Second stage was a very involved dissection requiring three hours
	16.0 p.o.	3	None	Very smooth; highest temperature 100.4° on eighth day	
6.0	16.8 h. 12.0 p.o.	6	Drug fever sixth day	Satisfactory	
	10.8 h. 17.0 p.o.	6	None	Smooth	
	24.0 p.o.	4	Jaundice on fourth day	Temperature elevated for 6 days	Cause of jaundice unknown; possibly sulfanilamide; cleared up after stopping drug
	22.4 h.	4	Anemia; slight jaundice; ? pulmonary infarct	Stormy 4 days; temperature to 102.4° second day	
4.0	9.6 h. 12.0 p.o.	6	Urinary retention and cystitis; drug fever fifteenth day (second course)	Temperature to 101.4° first day; normal after third until drug fever	
	17.3 h.	6	Acute anemia; ? drug fever	Late temperature rise to 102.4° on fourth and fifth days	Anemia and fever probably due to drug
	34.0 p.o.	8	Small hemorrhage in perineal wound	Smooth; temperature to 102° on second day	

TABLE

PROPHYLACTIC SULFANILAMIDE IN THE

HOSPITAL NO.	AGE	ADMISSION DATE	DATE OF DISCHARGE	DIAGNOSIS	OPERATION	
					DATE	TYPE
43181	53	10/21/39	11/25/39	Chronic ulcerative colitis; multiple polyposis	10/28/39	Ileostomy; resection right colon
43181	53	12/15/39	1/25/40	Chronic ulcerative colitis; multiple polyposis	12/19/39	Resection left colon
43211	36	10/25/39	12/13/39	Acute diverticulitis of cecum	10/25/39	Resection of cecum (Mikulicz)
36886	22	4/10/39	5/ 2/39	Terminal ileitis	4/13/39	Ileocolostomy, one stage; resection
42844	45	9/ 5/39	9/26/39	Terminal ileitis	9/ 9/39	Ileocolostomy, one stage; resection
41722	33	10/26/39	11/28/39	Lymphopathia venerea; previous colostomy	11/ 8/39	Resection of sigmoid and rectum

*h, Hypodermoclysis; *p.o.*, by mouth.

TABLE

PROPHYLACTIC SULFANILAMIDE

HOSPITAL NO.	AGE	ADMISSION DATE	DATE OF DISCHARGE	DIAGNOSIS	OPERATION	
					DATE	TYPE
39053	61	4/28/38	6/ 4/38	Acute sigmoid diverticulum; perforation following enema; generalized peritonitis; belly full of soapsuds	5/ 5/38	Colostomy with exteriorization of perforation
43157		9/12/39	10/21/39	Perforation of esophagus by esophagoscope; cardiospasm	9/12/39	Repair of perforation; splenectomy
42924	70+	9/16/39	10/ 9/39	Ruptured diverticulitis of right colon; diffuse peritonitis	9/16/39	Drainage
40982	52	12/27/38	1/10/39	Sigmoid diverticulitis; local peritonitis	12/27/38	Exploratory laparotomy and drainage
40220	8 mo.	8/30/38	9/ 6/38	Perforated Meckel's diverticulitis	8/30/38	Exploratory laparotomy; diverticulectomy; no drainage
40687	51	11/30/38	12/21/38	Acute sigmoid diverticulitis; local peritonitis	11/30/38	Drainage

*h, Hypodermoclysis; *p.o.*, by mouth.

IV

NONMALIGNANT LESIONS OF THE COLON

SULFANILAMIDE		DAYS OF DRUG	COMPLICATIONS	COURSE	REMARKS
PREOPERATIVE (GM.)	POSTOPERATIVE (GM.)*				
2.0	18.4 h. 3.0 p.o.	5	Phlebitis twelfth day day	No abdominal complications; up on tenth day	
	10.8	2	Infected wound	Febrile	
	23.2 h. 28.0 p.o.	3 7	? Pylephlebitis on fifth day; jaundice, chills and fever		Signs of pylephlebitis disappeared rapidly after resumption of sulfanilamide
	25.6 h. 4.0 p.o.	6	None	T.P.R. normal third day; very smooth	
	14.4	3	Minor wound infection	T.P.R. normal fourth day; very smooth	
5.0	6.4 h. 13.0 p.o.	5	Wound infection	Smooth	

V

IN BOWEL PERFORATIONS

SULFANILAMIDE		DAYS OF DRUG	COMPLICATIONS	COURSE	REMARKS
PREOPERATIVE (GM.)	POSTOPERATIVE (GM.)*				
	28.8 hypo. 5.0 p.o.	7	Drug fever fifth day	Temperature below 100° for five days	
	28.8 hypo.	3	Wound infection	Febrile	Culture: Hemolytic *Staph. aureus* and nonhemolytic streptococcus
	24.0 hypo.	5	Pelvic abscess (drained 10/5/39); cardiac failure	Gradual failure after three weeks; no peritonitis	Died
	16.6 h. 9.0 p.o.	6	None	Very smooth	Culture: staphylococcus
	7.2 h.	3	None	T.P.R. normal after third day; very smooth	Culture: staphylococcus
	17.6 hypo. 13.2 p.o.	7	None	Very smooth	Culture: Nonhemolytic streptococcus and *Str. viridans*

than the considerations of bacteriologic specificity. In peritonitis a minimal drug effect against the intestinal pathogens may serve to augment the natural defenses of the peritoneum to the extent that the balance of factors will become favorable to the host. There is no evidence available to justify the employment of sulfanilamide prophylactically or therapeutically to the exclusion of any other recognized principles or practices of therapy. We believe that the weight of experimental and clinical evidence now justifies the use of sulfanilamide as an adjunct to other forms of treatment in the management of threatened or established peritonitis of intestinal origin.

SUMMARY

1. In spite of important advances in technique peritonitis remains an important cause of death following operative procedures on the large intestine.

2. Peritonitis of intestinal origin is a polymicrobic infection, and the bacteria concerned in its production are relatively, but not entirely, resistant to sulfanilamide bacteriostasis.

3. This bacteriostatic effect may become significant in the peritoneal defense against postoperative peritonitis if an adequate concentration of drug is present, if the number of contaminating organisms is small, if tissue necrosis is minimal, and if the usual cellular defense is present.

4. Clinical experience is as yet insufficient to warrant final conclusions as to the effectiveness of sulfanilamide in the prevention of peritonitis.

5. A series of sulfanilamide-treated cases is presented in which it is suggested that the drug may safely be used in conjunction with other therapeutic measures of recognized value. None of these cases showed evidence of spreading peritonitis after the institution of sulfanilamide therapy.

REFERENCES

1. Wilkie, D. P. D.: Cancer of the Colon; Its Surgical Treatment, Lancet **1**: 65, 1934.
2. Patterson, H. B., and Webb, A., Jr.: The Mikulicz Procedure, Ann. Surg. **111**: 64, 1940.
3. Stone, H., and McLanahan, S.: Carcinoma of the Large Bowel, Surgical Aspects, J. A. M. A. **113**: 2282, 1939.
4. Mayo, C. W., and Simpson, W. C.: Surgical Procedures for Carcinoma of the Transverse Colon, Ann. Surg. **109**: 430, 1939.
5. Allen, A. W.: Right Colectomy for Malignant Disease, J. A. M. A. **109**: 923, 1937.
6. MacFee, W. F.: Resection With Aseptic End-to-End Anastomosis for Carcinoma of the Colon, Ann. Surg. **106**: 701, 1937.
7. Rankin, F. W.: Mortality Following Colostomy for Carcinoma of the Large Bowel, Ann. Surg. **89**: 62, 1929.
8. Ochsner, A., and DeBakey, M.: Operability, Morbidity and Mortality Factors in Carcinoma of the Colon, Am. J. Surg. **46**: 103, 1939.
9. Lockwood, J. S., Coburn, A. F., and Stokinger, H.: Studies in the Mechanism of the Action of Sulfanilamide, the Bearing of the Character of the Lesion on the Effectiveness of the Drug, J. A. M. A. **111**: 2259, 1938.

10. Meleney, F. L., Harvey, H. D., and Zaytseff-Jern, H.: Peritonitis. I. The Correlation of the Bacteriology of the Peritoneal Exudate and the Clinical Course of the Disease in 106 Cases of Peritonitis, Arch. Surg. **22**: 1, 1931.
11. Meleney, F. L., Olpp, J., Harvey, H. D., and Zaytseff-Jern, H.: Peritonitis, Synergism of Bacteria Commonly Found in Peritoneal Exudate, Arch. Surg. **25**: 709, 1932.
12. Coller, F., Ransom, H. K., and Rife, C. S.: Experimental Studies on Reactions of the Peritoneum to Trauma and Infection, Arch. Surg. **39**: 761, 1939.
13. Gay, F. P.: A Histologic Basis for Local Resistance and Immunity to Streptococcus, Arch. Path. **1**: 857, 1926.
14. Steinberg, B.: Experimental Background and Clinical Application of *E. coli* and Gum Tragacanth Mixture (Coli-Bactragen) in Prevention of Peritonitis, Am. J. Clin. Path. **6**: 253, 1936.
15. Dixon, C. F.: Discussion of Papers on Peritonitis, Arch. Surg. **39**: 780, 1939.
16. Rankin, F. W.: Resection of Rectosigmoid by Single or Graded Procedures, Ann. Surg. **104**: 628, 1936.
17. Coller, F. A., and Rife, C. S.: Immunization of the Peritoneum, Am. J. Surg. **46**: 61, 1939.
18. Ravdin, I. S., Rhoads, J. E., and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated With Appendicitis, Ann. Surg. **111**: 53, 1940.
19. Lockwood, J. S., and Lynch, H. M.: The Influence of Proteolytic Products on the Effectiveness of Sulfanilamide Action, J. A. M. A. **114**: 935, 1940.
20. Miller, C. P.: A Study of Experimental Meningococcal Infection. Method, Proc. Soc. Exper. Biol. & Med. **32**: 1136, 1935.
21. Bieter, R. N., Larsen, W. P., Levine, M., and Cranston, E. M.: Protective Action of Sulfapyridine Against Type II Pneumococcal Infections in Mice, Proc. Soc. Exper. Biol. & Med. **41**: 202, 1939.
22. Corry, D. C., Brewer, A. C., and Nicol, C.: Postoperative Treatment of Appendicular Peritonitis With Sulfanilamide and Its Derivatives, Brit. M. J. **2**: 561, 1939.
23. Steinberg, B.: Stages in Peritonitis Based on Defense Mechanism in Relation to Treatment, Arch. Surg. **39**: 770, 1939.
24. Lockwood, J. S., and Rhoads, J. E.: The Use of Sulfanilamide in the Treatment of Peritonitis, S. Clin. North America **21**: 1457, 1939.
25. Ottenberg, R., and Berck, M.: Sulfanilamide Therapy for Suppurative Pylephlebitis and Liver Abscesses, J. A. M. A. **111**: 1374, 1938.

THE REPAIR OF TRACHEAL AND BRONCHIAL DEFECTS WITH FREE FASCIA GRAFTS

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IN 1909 Kirschner[4] published his first extensive communication describing the many possible uses of free homologous grafts of fascia. In the immediately subsequent years Hohmeier,[2, 3] Davis,[1] Kostenko and Rubaschew,[5] and Neuhof[8] reported experimental studies where free grafts of fascia had been employed to cover defects in the cervical trachea. A window of varying size was made in the anterior wall of the trachea and this was at once covered with a rectangular flap of fascia sewn securely in place at the margins of the defect. In addition Hohmeier[3] performed tracheotomies in two of his animals, and, after a period of twelve and thirteen days respectively, débrided the slightly infected edges of the tracheal opening and sutured a patch of fascia over it. The wounds in both instances healed per primam. Hohmeier[2, 3] alone derived his grafts from the fascia of the sternocleidomastoid muscle. The other authors turned to the fascia lata. In 1912 Levit[6] and later Lucas[7] and Neuhof[8] each reported a clinical case of a long-standing tracheal fistula which had been successfully repaired with a segment of fascia lata.

The purpose of these experiments was to reopen the subject concerning the employment of fascia grafts in repairing defects of the respiratory tree, to study histologically and at varying time intervals the nature of the repair, and to determine whether such a graft could be utilized in the closure of tracheal and bronchial defects within the thorax. Four series of experiments were carried out, all in dogs: (I) Repair of cervical tracheal defects; (II) repair of bronchial defects; (III) repair of bronchial defect after lobectomy; (IV) repair of tracheal defect after total pneumonectomy.

Series I. Repair of Cervical Tracheal Defects (Six Animals).—Under intravenous nembutal anesthesia the trachea was exposed through a midline incision in the lower neck. A rectangular full thickness segment of the anterior tracheal wall, measuring 1 by 1 cm. and including arcs of one or two tracheal rings, was excised. The open window was covered with a slightly larger free patch of deep cervical fascia which was sutured to the outer surface of the trachea at a distance of about 3 mm. from the margins of the defect. The sutures did not penetrate the lumen of the trachea and were placed in such a way as to make the fascia span tightly across the defect. There was thus no fluttering of the graft with the phases of respiration. Interrupted sutures of fine

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black silk placed closely together were used. An airtight closure, determined by flooding the wound with salt solution, was obtained in each instance, and the wound was sutured in layers without drainage. All the animals survived the procedure and remained perfectly well throughout the duration of the experiments. The wounds healed per primam. In no instance were any respiratory complications or subcutaneous emphysema noted. The animals were sacrificed at the end of one, two, three, four, eight, and twelve weeks respectively. Immediately before death, the wounds in the neck were opened and the operative sites in the trachea exposed. The new tissue filling the defect in each instance was firm and did not flutter.

Dog 429 was sacrificed after one week. *Gross Findings.*—The pretracheal muscles are loosely adherent to the trachea at the site of the defect. The graft is easily identified and is firmly in place. It has lost the usual appearance of fascia and now presents as a flat sheet of semiopaque brown-red finely granular tissue completely covering the tracheal defect and projecting hardly at all into the lumen of the trachea. The inner aspect of the graft is bare and naked of epithelium except at its very borders where a thin edge of new epithelium is growing in from the tracheal mucosa. The rest of the trachea, the bronchi, and the lungs in this animal as well as in all the others in this series reveal no evidence of any inflammatory reaction.

Microscopic Findings.—The graft appears to have lost its usual cytological architecture and is represented as a poorly delimited sheet of homogeneous pink-staining tissue containing scattered pyknotic vestiges of former nuclei. Invading the periphery of the graft and completely covering its external surface is a rich growth of fibroblasts which contains within it many newly formed, thin-walled blood vessels and a heavy sprinkling of polymorphonuclear leucocytes and round cells. The central core of the graft is as yet free from this invasion. The luminal surface is covered with a layer of fibrin sparsely infiltrated with polymorphonuclear leucocytes. There is some regeneration of the mucosa at the edges of the defect. The new epithelial cells are flatter than usual, and no cilia are seen. Two silk sutures, cut in cross section, are surrounded by a thin wall of fibroblasts and leucocytes.

Dog 428 was sacrificed after two weeks. *Gross Findings.*—The trachea is not unduly adherent to the adjacent muscles. The defect is completely covered by red, granular, vascular tissue. The epithelium, which has now regenerated over the entire inner surface of the graft, appears to be definitely thinner than that of the adjacent mucosa. The defect has not shrunken appreciably in size, and there is at no point any diminution in the caliber of the trachea.

Microscopic Findings.—The epithelium has completely regenerated and covers the entire defect except at one point near its center where

it appears to have been brushed away in the process of preparing the section. The cells are flat to cuboidal. Definite cilia are seen in the new mucosa, but these are sparse. No submucous glands are present. The original graft is not recognizable, and the defect is filled with a thick vascular layer of fibroblasts which are beginning to resemble adult connective tissue cells. There is a scattered infiltration everywhere, including the new mucosa, of polymorphonuclear leucocytes and round cells. This is most marked in the outer surface of the trachea, well outside the zone of the defect, where several small and large clusters of leucocytes and fibroblasts encapsulate the cut ends of silk sutures. Here occasional multinucleated giant cells are seen. New budding cartilage cells are growing from the cut ends of the rings adjacent to the defect.

Dog 425 was sacrificed after three weeks. *Gross Findings.*—The tracheal window, unaltered in its dimensions, is closed with a firm layer of pale red tissue which does not project into the lumen of the viscus. The epithelium has completely regenerated. There appear to be no remains of the original fascial stamp.

Microscopic Findings.—No definite traces of the graft can be discerned. The defect is bridged with a layer of loose vascular areolar tissue which now closely resembles adult connective tissue. The cellular infiltration is still present but is very much diminished in extent. On the outer surface of the trachea at some distance from the edge of the defect a few large clusters of polymorphonuclear leucocytes are present. Silk strands are found within some of these. The mucosa has completely regenerated. The cells are flat to cuboidal in shape, but abundant cilia are present. A few subepithelial mucous glands and three small islands of young cartilage cells are in evidence in the new subepithelial connective tissue near the borders of the defect.

Dog 423 was sacrificed after four weeks. *Gross Findings.*—The defect is well covered with a pale white tissue resembling connective tissue. The mucosal surface of the trachea everywhere appears to be normal and intact.

Microscopic Findings (Fig. 7).—No distinct traces of the graft are present. There is complete regeneration of the epithelium which is arranged in the typical pseudostratified formation and is no longer distinguishable from the normal previously intact epithelium. Filling the defect is a layer of well-differentiated adult connective tissue scattered within which are a moderate number of blood vessels and occasional areas of differentiating fibroblasts. The cellular infiltration is still present, but it is not conspicuous. Foreign body reactions are seen surrounding fragments of silk sutures in the outer tracheal wall. There are a few islands of regenerating cartilage cells and mucous glands in the new submucosa.

Dog 422 was sacrificed after eight weeks. *Gross Findings.*—The pretracheal muscles are quite adherent to the trachea. The defect is filled with a thin layer of white avascular translucent tissue. The epithelium is intact.

Microscopic Findings.—Normal adult relatively avascular connective tissue spans the defect. Cellular infiltration is minimal. The new mucosal lining is made up of the usual ciliated tracheal epithelium with an abundance of globlet cells. Some silk strands encapsulated by connective tissue cells are seen. A few scattered fibers of the adherent pretracheal muscles are noted.

Dog 374 was sacrificed after twelve weeks. The gross and microscopic (Fig. 11) findings are essentially identical to those described in Dog 422.

Series II. Repair of Bronchial Defects (Six Animals).—Under intravenous nembutal anesthesia supplemented with intermittent administration of positive pressure through an inlying intratracheal tube, the left hemithorax was entered through an incision in the fourth left interspace anteriorly. The main left upper lobe bronchus was identified and a full thickness rectangular segment measuring 0.5 by 0.5 cm. excised. The defect was bridged in the same manner as described in Series I with a free flap of deep fascia removed from the chest wall, care being taken to ensure an airtight closure. In some instances a small bit of striated pectoral muscle was applied to reinforce the closure. The left lung was then expanded and the wound in the pleura and chest wall closed without drainage. All the animals survived the procedure. The wounds healed per primam. No respiratory difficulties of any nature were encountered. There were no instances of hydrothorax, pyothorax, or tension pneumothorax. The animals were sacrificed at the end of one, two, three, four, eight, and twelve weeks respectively. Before removing the anterior chest wall, the lungs were inflated in situ with air, and the trachea clamped. The same gross findings were observed in the six animals of the series. All the lobes of the lungs were fully and normally expanded and filled their respective pleural cavities. The left upper lobe was pink and crepitant with no foci of atelectasis or pneumonic infiltration. There was no free fluid in either pleural cavity. The wound in the parietal pleura at the fourth left interspace healed well and did not become adherent to the left lung. The lungs and tracheobronchial tree were removed en masse. A solution of 10 per cent formalin was injected into the trachea in an amount sufficient to distend the lungs to approximately their usual size within the thoracic cavity. The trachea was then ligated and the entire pulmonary system submerged in formalin and allowed to fix.

Dog 411 was sacrificed after one week. *Gross Findings.*—There is no encroachment of the left upper lobe bronchial lumen at the site of the defect. The graft can be recognized, but it is dull, opaque and granular

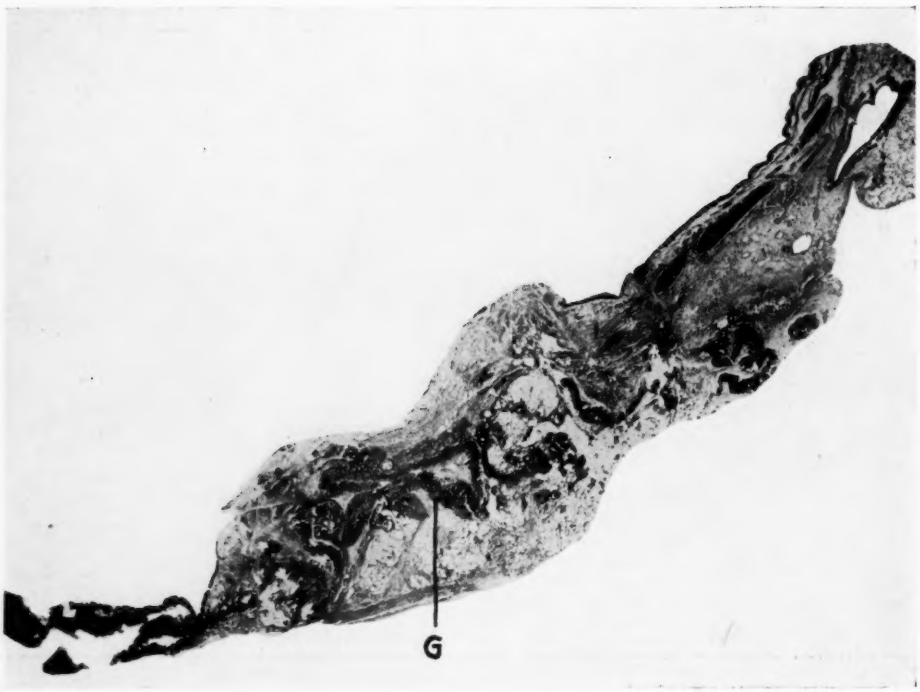

Fig. 1.—Dog 411. Bronchus window (one week). Graft (*G*) visible as wavy, opaque fragmented structure surrounded by proliferating fibroblasts, inflammatory cells, and adipose tissue. Early regeneration of the mucosa is noted at the edges of the defect. (×6.)

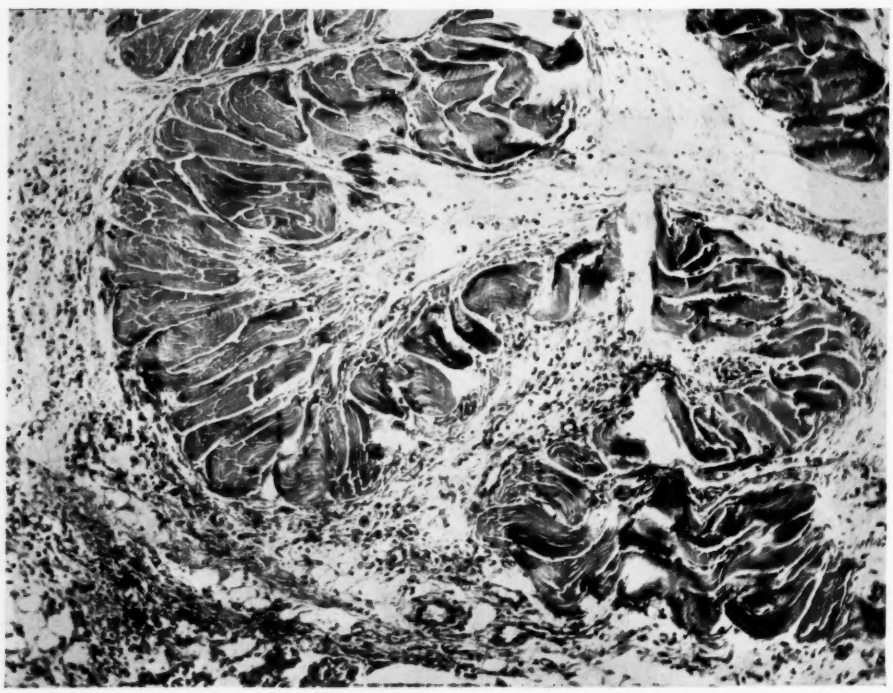

Fig. 2.—Dog 411. Bronchus window (one week). Graft is dull and fragmented and appears hyalinized. Growing into it from all sides are fibroblasts infiltrated with polymorphonuclear leucocytes and round cells. (×75.)

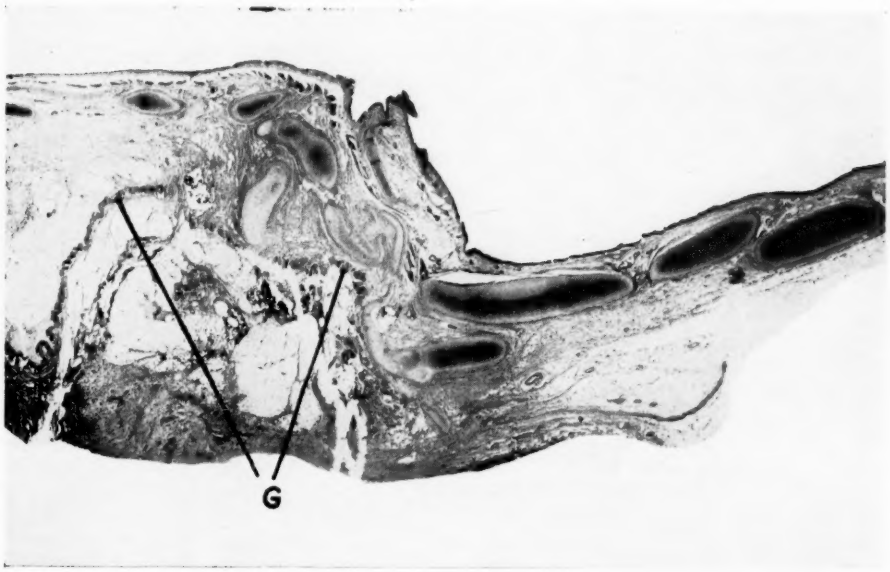

Fig. 3.—Dog 417. Lobectomy (one week). Epithelium completely regenerated. Marked proliferation of new cartilage. Remainder of defect filled with granulation tissue and fat-containing cells. Graft (*G*) presents as thin, wavy, shredded structure. (×6.5.)

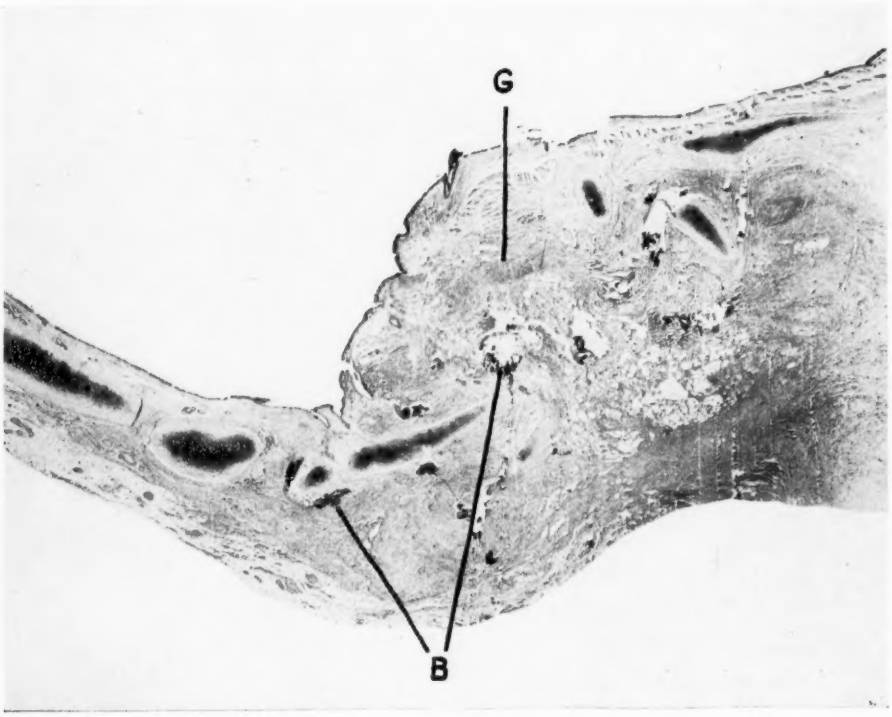

Fig. 4.—Dog 416. Lobectomy (two weeks). Mucosa regenerated. Graft (*G*) being invaded and replaced by fibroblasts. Defect filled with differentiating fibroblasts and islands of adipose tissue. Silk sutures (*B*). (×7.5.)

and does not resemble the former pale stamp of connective tissue. The mucosal surface of the graft is raw and covered with fibrin.

Microscopic Findings (Figs. 1 and 2).—The graft is easily identified and does not appear to be viable. It takes a diffuse homogeneous pink stain and contains scarce nuclear elements. It is surrounded by a layer of invading fibroblasts and young, newly formed blood vessels. A marked infiltration of polymorphonuclear leucocytes and round cells is present in these invading zones as well as among the fibroblasts surrounding strands of silk sutures. There are scattered groups of large fat-containing cells. Early and limited regeneration of epithelium is noted only at the margins of the defect, while the inner aspect of the remainder of the graft is covered with very vascular granulation tissue over which lies a sheet of fibrin heavily infiltrated with white cells.

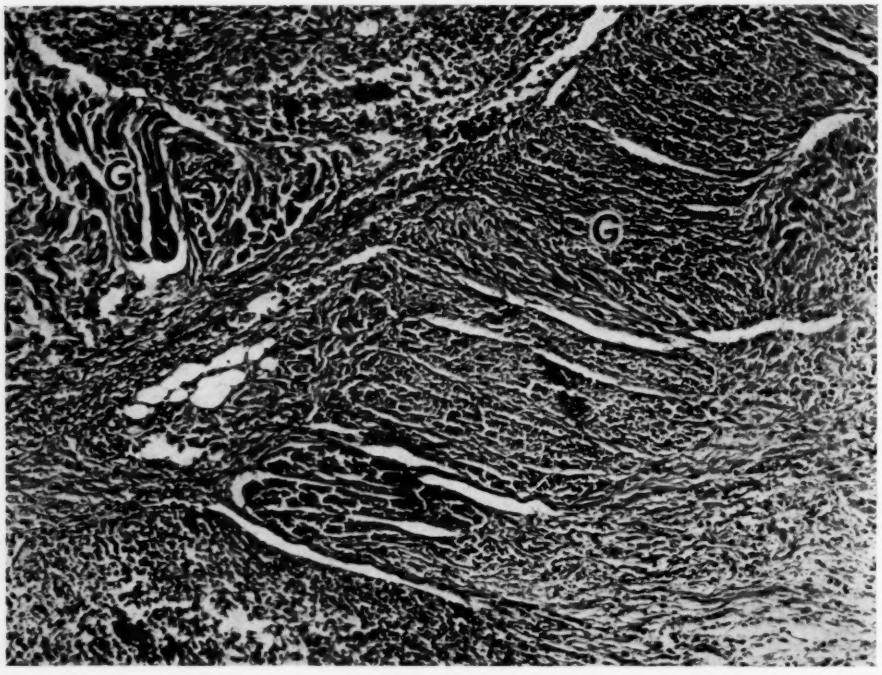

Fig. 5.—Dog 410. Bronchus window (two weeks). Graft (*G*) with outlines poorly defined, being replaced by proliferating fibroblasts. (×125.)

Dog 410 was sacrificed after two weeks. *Gross Findings.*—The bronchial lumen is free and not constricted. The graft cannot be recognized, and the gap is filled with a flat layer of brown-red vascular tissue. The bronchial mucosa is everywhere intact.

Microscopic Findings (Fig. 5).—The mucosa is completely regenerated. It is composed of pseudostratified ciliated columnar epithelium and contains many goblet cells. Beneath this new mucosa is a layer of fibroblasts loosely arranged and harboring within it many thin-walled blood vessels and few leucocytes. There is no evidence of regeneration

of the muscularis mucosa. The fascia graft is fragmented, takes a homogeneous pink stain, and appears hyalinized. Each fragment is surrounded and invaded by fibroblasts heavily infiltrated with polymorphonuclear leucocytes and round cells. A few strands of silk are similarly being invaded. Several clusters of fat-containing cells are present.

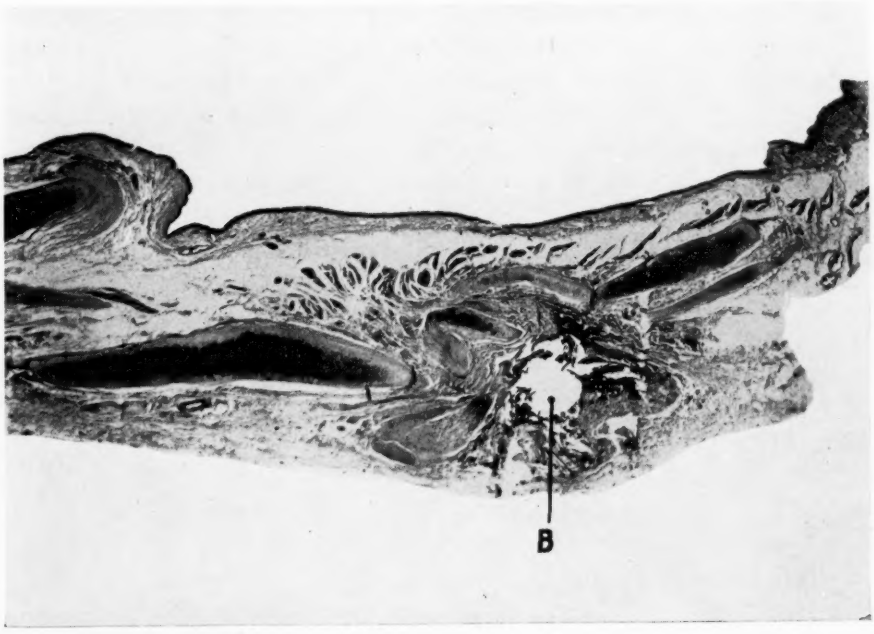

Fig. 6.—Dog 414. Lobectomy (three weeks). Mucosa regenerated. Smooth muscle cells in submucosa are prominent. New islands of cartilage are present. *B* represents shredded black silk suture. There is no evidence of graft. (×17.)

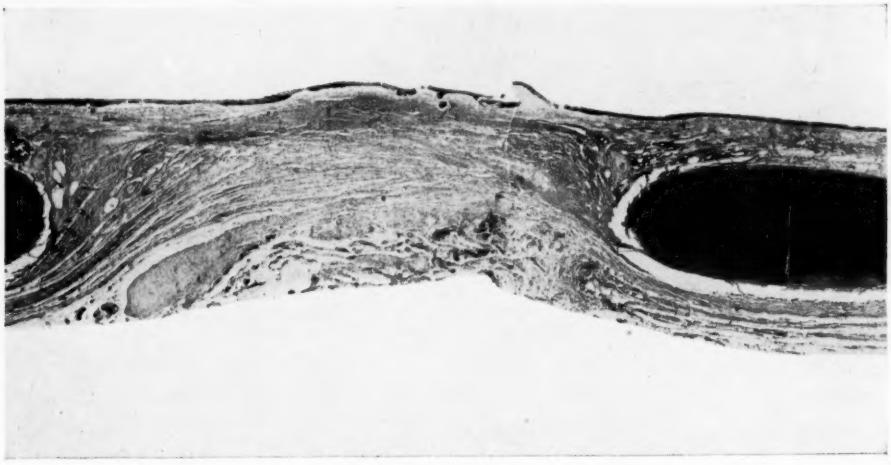

Fig. 7.—Dog 423. Tracheal window (four weeks). Respiratory epithelium completely regenerated. Defect filled with differentiated adult connective tissue. Cellular infiltration not prominent. (×11.)

Dog 409 was sacrificed after three weeks. *Gross Findings.*—The lumen of the bronchus is not narrowed. The original defect appears to be shrunken somewhat in size and is covered with a sheet of red-brown tissue, the inner surface of which is completely epithelialized.

Microscopic Findings.—The pseudostratified ciliated columnar epithelium is completely regenerated and rests upon a layer of young connective tissue cells. No muscularis mucosa is present here. In the area of the defect there are scattered fragments of thin viable adult connective tissue which are partially encircled by fibroblasts and fat-containing cells. These fragments appear to be the remains of the original graft which have "taken." The cellular infiltration is in general less conspicuous, while scattered foreign body multinucleated giant cells are present in large numbers within islands of granulation tissue near strands of silk. At the borders of the defect there are a few small scattered clumps of young cartilage.

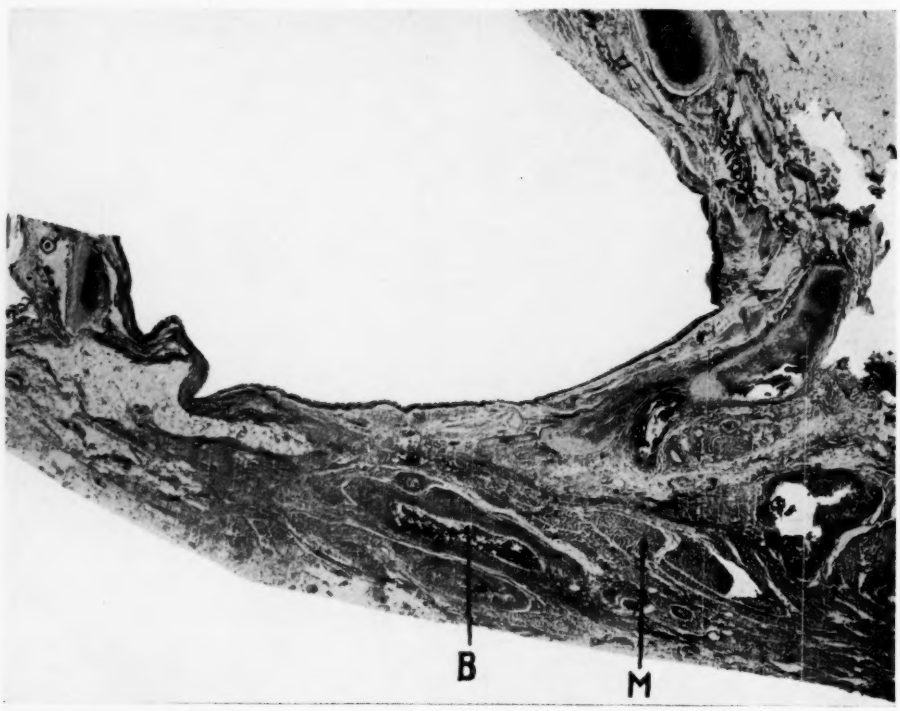

Fig. 8.—Dog 407. Bronchus window (four weeks). Mucosa intact and rests on layer of connective tissue. Fibroblasts and wandering cells noted chiefly around sutures (*B*). Well-stained fibers of striated muscle (*M*) are present. (×12.)

Dog 407 was sacrificed after four weeks. *Gross Findings.*—The mucosa is intact. The defect is spanned by a thin layer which resembles connective tissue in its gross characteristics.

Microscopic Findings (Fig. 8).—Under the completely regenerated epithelium there is a layer of normal adult connective tissue and a moderate amount of adipose tissue. Mucous glands and a few islands

of young cartilage cells are present in the new submucosa, but no smooth muscle elements can be clearly recognized. The cellular infiltration is almost completely absent and, together with differentiating fibroblasts, is limited to the areas immediately adjacent to strands of silk. At one point near the border of the defect some viable, well-stained fibers of striated muscle are noted.

Dog 398 was sacrificed after eight weeks. *Gross Findings.*—A thin layer of translucent connective tissue which contains elements of cartilage spans across the defect. The mucosa is intact.

Microscopic Findings (Fig. 9).— A layer of adult connective tissue fills the defect. In addition there is a striking proliferation of young cartilage cells which have overgrown from the edges and almost meet in the center of the defect. The epithelium is ciliated and completely regenerated. The submucosa is composed of connective tissue and contains mucous glands but no smooth muscle. Silk strands encapsulated by a thin collar of connective tissue and small round cells are present.

Fig. 9.—Dog 398. Bronchus window (eight weeks). Mucosa regenerated and lifted by marked overgrowth of new cartilage. Adult connective tissue present everywhere except immediately adjacent to black silk sutures where few fibroblasts are still noted. (×9.)

Dog 387 was sacrificed after twelve weeks. The gross and microscopic (Fig. 12) findings are essentially the same as those described for Dog 398. The marked proliferation of cartilage is not noted here. There is no evidence of any new growth of the muscularis mucosa.

Series III. Repair of Bronchial Defect After Lobectomy (Six Animals).—The anesthesia and operative approach were the same as those described in Series II. The left upper lobe pulmonary arteries and veins were isolated, doubly ligated, and divided. A clean transection of the left upper lobe bronchus was made exactly at its bifurcation from the

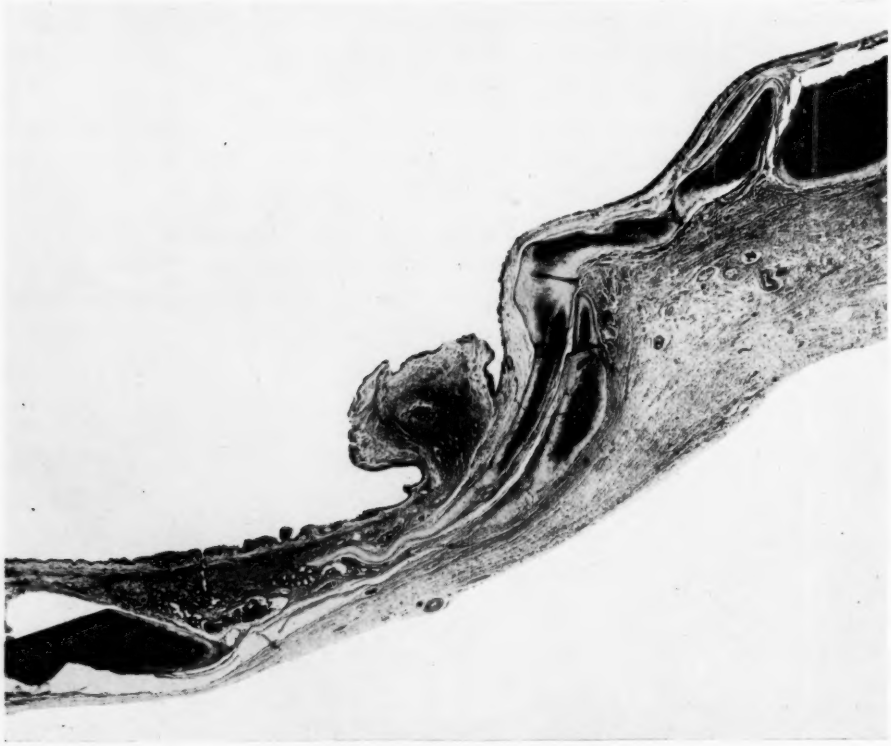

Fig. 10.—Dog 426. Pneumonectomy (eight weeks). Defect spanned by connective tissue into which there has grown at one side a tongue of new cartilage. Mucosa intact. The projecting submucosal tuft of granulation tissue harbors a silk suture in its center. (×11.)

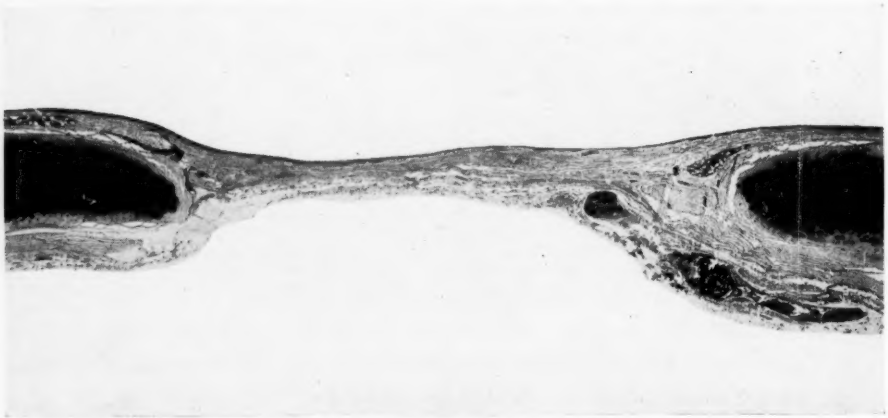

Fig. 11.—Dog 374. Tracheal window (twelve weeks). Mucosa intact and resting upon layer of connective tissue. A few sutures are seen. (×11.)

left main bronchus and the left upper lobe was removed. A patch of deep thoracic fascia was sewn securely over the open hole, care being taken to make the closure airtight. The left lower lobe was allowed to expand, and the wound in the chest wall was repaired in layers without drainage. The dogs survived the procedure without developing any complications. The wounds healed per primam. No respiratory difficulties were encountered at any time. The animals were sacrificed at the end of one, two, three, four, eight, and twelve weeks respectively. As in Series II, the lungs were inflated in situ with air and the trachea clamped, prior to opening the thoracic cage. All the animals exhibited essentially the same gross findings. The empty nest of the left upper

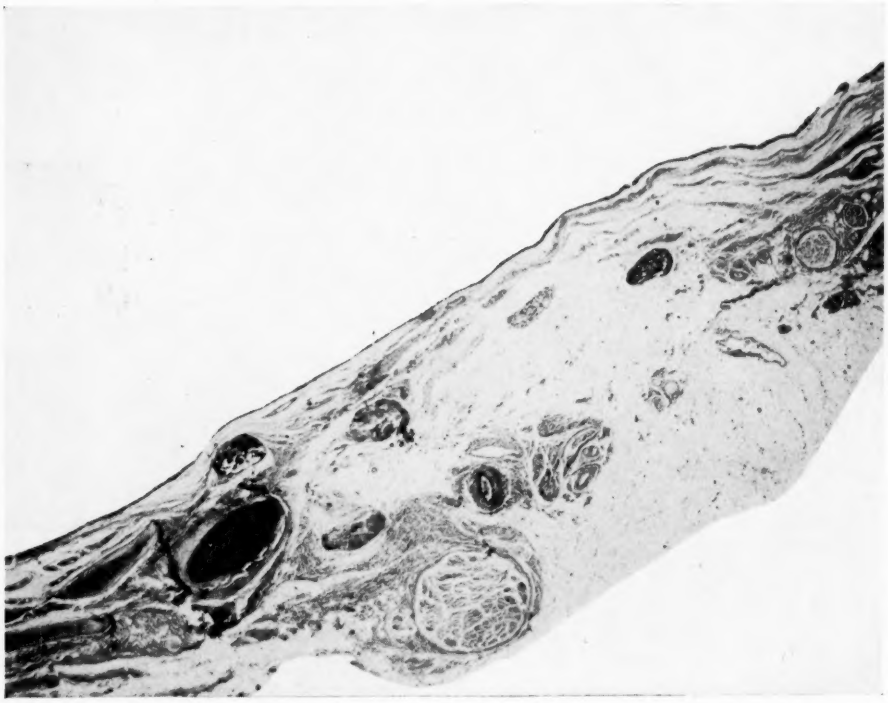

Fig. 12.—Dog 387. Bronchus window (twelve weeks). Normal mucosa and connective tissue across defect. (×17.)

lobe was filled in part by the overexpanded left lower lobe and in part by the similarly overexpanded right upper lobe which, together with its adjacent mediastinum, had crossed the midline and herniated into the left upper thoracic cavity. These changes in the realignment of the lobes of the lung were noted as early as one week after the operation and were indeed almost complete at that time. The left lower lobe was always well expanded and revealed no evidence of inflammatory infiltration. No blood or free fluid was found in either of the pleural cavities. There were no adhesions between the left lower lobe and the parietal pleural wound. After removal from the thorax the lungs were inflated with 10 per cent formalin and fixed in this position.

The gross and microscopic findings in this group were essentially the same as those noted in Series II and therefore will not be described in detail. There appeared in this third series to be a greater shrinkage of the size of the defect than was observed in either of the other two groups. Regeneration of the mucosa was complete by the end of the first week (Fig. 3). The epithelium was ciliated and pseudostratified, and contained numerous goblet cells. In addition there seemed to be a greater growth of new cartilage, which for the first time seemed to take an active part in filling the defect. The muscularis mucosa was quite abundant in the new submucosa, but whether this was due to an actual proliferation of smooth muscle cells or to their possible displacement from the adjacent normal submucosa could not be determined. The progressive changes in the graft were the same as those described previously. The animals in this group were Dogs 417, 416 (Fig. 4), 414 (Fig. 6), 413, 412, and 406 (Fig. 13).

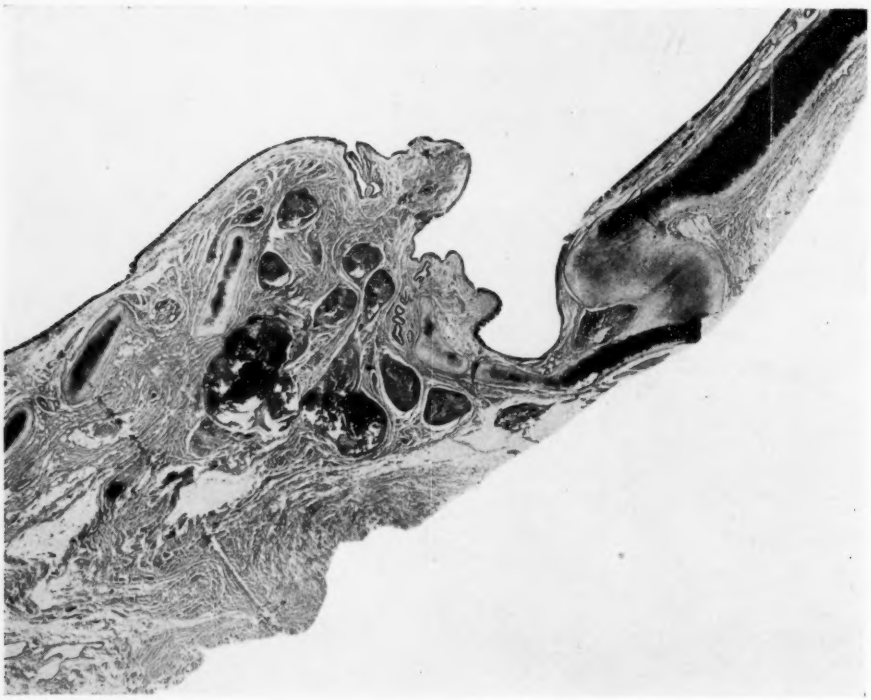

Fig. 13.—Dog 406. Lobectomy (twelve weeks). Regenerated mucosa covering thick layer of connective tissue. The many silk sutures cut in cross section are surrounded by thin collars of differentiating fibroblasts and wandering cells. (×11.)

Series IV. Repair of Tracheal Defect After Total Pneumonectomy (Two Animals).—The anesthesia and the operative approach were the same as those described in Series II and III. The left main pulmonary arteries and veins were isolated, separately ligated, and divided. The main left bronchus was transected exactly at the point where it branched

off from the trachea, and the left lung was removed. No bronchial stump remained. A stamp of deep thoracic fascia was sewn securely over the open defect in the trachea, and the wound in the chest wall was closed without drainage. Both animals survived the procedure and made uneventful recoveries. The wounds healed per primam. The animals were sacrificed at the end of eight and twelve weeks respectively.

Dog 426 was sacrificed after eight weeks. At autopsy the right lung was inflated with air, and the trachea was ligated in the neck before removal of the chest wall.

Gross Findings.—The left diaphragm is elevated, and the bony thoracic wall on this side is slightly shrunken. The heart lies entirely within the left hemithorax. The remainder of this half of the thoracic cavity is filled largely with the overexpanded right upper lobe which has herniated across the midline, and to a lesser extent with the overexpanded right lower and mediastinal lobes. There is no free fluid within the pleural cavities. The wound in the left parietal pleura is completely healed and is not adherent to any of the underlying thoracic viscera. The lobes of the right lung are all overexpanded and are soft and crepitant throughout. The defect at the bifurcation of the trachea is spanned by a layer of brown-red translucent tissue, the inner aspect of which is completely epithelialized. There is at no point any appreciable encroachment upon the lumen of the trachea or the right main bronchus.

Microscopic Findings (Fig. 10).—The ciliated pseudostratified epithelium is completely regenerated. The submucosa is moderately thick and contains many mucous glands and a heavy infiltration of polymorphonuclear leucocytes and round cells. The inflammatory cells are prominent chiefly in the neighborhood of the sutures. External to the submucosa is a relatively avascular layer of adult connective tissue cells and new cartilage. The original graft cannot be recognized. A small submucosal tuft of granulation tissue with a silk suture at its core is noted.

Dog 424 was sacrificed after twelve weeks. The gross findings are the same as those described for Dog 426. On microscopic examination the defect is found to be covered with a layer of adult connective tissue cells. Cellular infiltration is scant and inconspicuous. The normal respiratory mucosa is completely regenerated. A few scattered mucous glands are present in the submucosa and occasional black silk sutures are noted.

SUMMARY AND CONCLUSIONS

Free fascia grafts have been successfully employed in dogs to repair defects in the trachea and bronchi after local resection of full thickness segments of these viscera as well as after lobectomy and total pneumonectomy. The twenty animals investigated all survived the operative procedure and remained entirely well throughout the duration of the experi-

ment. The wounds healed per primam. There were no instances of subcutaneous emphysema, pneumothorax, hydrothorax, or pleural empyema. None of the animals developed any pulmonary parenchymal complications that could be detected during life or at autopsy. A moderate diminution in the size of the defect was noted only in the lobectomy experiments. In the other series the original measurements of the defect remained essentially unchanged. There was in none of the animals any appreciable encroachment upon the caliber of the trachea or bronchus at the site of the application of the graft.

The healing process followed essentially the same pattern whether the defect was in the trachea or the bronchus. The graft did not appear to remain viable but acted rather as a temporary and airtight scaffold quickly to be invaded and replaced by wandering cells and proliferating fibroblasts. The latter in turn became differentiated into collagen-bearing adult connective tissue which remained as a permanent supporting structure spanning the defect. Regeneration of the respiratory mucosa, already in evidence at the borders of the defect after one week, was complete at the end of the second week. The cells, at first cuboidal in shape and sparsely ciliated, quickly assumed the pseudostratified appearance and acquired their normal complement of cilia and goblet cells. In one instance (Dog 417, lobectomy) complete epithelialization occurred within one week. Mucous glands were noted in the new submucosa after the third week. There was no clear evidence in any of the sections of regeneration of the muscularis mucosa. Budding young cartilage cells were observed in the cut ends of the tracheal and bronchial rings. These islands of new cartilage, however, with a few notable exceptions, appeared to take little part in filling the original defect. The silk sutures were at the outset encapsulated by fibroblasts and wandering cells, and later by a thin shell of adult connective tissue. All phases of healing were practically complete during the fourth week after the application of the graft. The new and final structures which served to restore the continuity of the viscus were composed of (1) an inner layer of pseudostratified ciliated epithelium; (2) a layer of submucosa with occasional mucous glands and a few small islands of new cartilage but, with occasional exceptions, no fibers of muscularis mucosa; and (3) an outer layer of supporting adult connective tissue.

There are obvious inherent advantages in a method which provides an airtight and adequate closure of an open defect in the wall of a hollow semirigid respiratory tube without the necessity of approximating the free edges of the defect to each other and without constricting to any appreciable degree the caliber of the viscus. Certain clinical applications of this method at once suggest themselves. Its usefulness in the repair of old tracheotomy wounds in man has already been pointed out. Small benign and early malignant lesions of the trachea, which for one reason or another cannot be adequately treated through

the bronchoscope, may be resected and the opening covered with a stamp of fascia. Similarly benign lesions of the larger bronchi may be excised locally and the remaining defect closed with fascia, thus obviating the necessity of extirpating the accompanying normal pulmonary lobe. Its greatest field of usefulness appears at the moment to be in those instances of lobectomy or total pneumonectomy where it is necessary to transect the bronchus exactly at its point of bifurcation from the main bronchus or the trachea respectively and where no long bronchial stump is left that can be closed by the usual methods. The closure of such an opening by suturing the edges to each other may not only be difficult technically because of the rigidity of the viscus, but may result in a serious kinking and obstruction at the site of the suture. Finally free fascia grafts may be employed to advantage to cover and reinforce ordinary suture lines in the trachea or larger extrapulmonary bronchi. Fascia is present everywhere in abundance, and an amount sufficient for a free graft is readily available in the local operative wound.

REFERENCES

1. Davis, J. S.: The Transplantation of Free Flaps of Fascia, Ann. Surg. **54**: 734, 1911.
2. Hohmeier, F.: A New Procedure for Closing Tracheal Defects, Münch. Med. Wchnschr. **58**: 948, 1911.
3. Hohmeier, F.: Experiments on Free Auto-Grafts, Verhandl. d. deutsch. Gesellsch. f. Chir. **40**: 111, 1911.
4. Kirschner, M.: Concerning the Use of Free Fascia Grafts, Beitr. z. klin. Chir. **65**: 472, 1909.
5. Kostenko, M. F., and Rubaschew, S. M.: Concerning Free Fascia Transplants, Zentralbl. f. Chir. **39**: 1448, 1912.
6. Levit, H.: Repair of Tracheal Defects With Free Grafts of Fascia Lata Femoris, Arch. f. klin. Chir. **97**: 686, 1912.
7. Lucas, H.: Concerning the Use of Free Fascia Lata Grafts, Arch. f. klin. Chir. **100**: 1129, 1913.
8. Neuhof, H.: Fascia Transplantation Into Visceral Defects, Surg., Gynec. & Obst. **24**: 383, 1917.

IS THE CONSERVATIVE TREATMENT OF INFECTION OR GANGRENE IN DIABETIC PATIENTS WORTH WHILE?

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THE conservative treatment of peripheral arterial disease seeks to avoid leg amputation. This objective has been held by members of our surgical staff who were interested in the subject, and any method which offered hope of improvement was tried. This has been of obvious benefit in some disorders but has not been so apparent in the diabetic group, for these patients have many complicating factors present that may influence the outcome. It was considered desirable to appraise our results in patients with diabetes.* We wished to see when and where our treatment was satisfactory, how it could be improved, where it had failed, and how the failures could be avoided. These data are presented, without comparative analysis or review of the literature, only to show our experience and to act as a guide for the future in the management of these cases.

CLASSIFICATION OF PATIENTS

There is a great deal of confusion in the literature on diabetic gangrene because of the failure to classify the cases into comparable groups in which all circumstances are uniform. This is a primary necessity for study; otherwise, statistics are meaningless. The factors that were considered important to determine in each case were the age and general condition of the patient, the duration, severity, and control of the diabetes, the state of the systemic circulation, the type and virulence of the infecting organism, the extent of spread of the infection and its local and general effect upon the patient, the cause, duration, site, type, and extent of the local lesion, and, most important, the degree of circulatory damage.

When these data were recorded and studied, it was found that the extent and virulence of the infection and the degree of circulatory damage were the two which most obviously influenced the course and the result. The others entered into consideration less often than was anticipated.

The cases were divided into those with a normal, good, fair, and poor circulation. Those placed in the group of poor circulation had a severely damaged and often hopelessly inadequate circulation in the feet. They had symptoms of claudication and rest pain, a cold, discolored, pulseless

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foot, trophic changes of skin and nails, absence of a pulse in the popliteal artery, extreme calcification of the vessels in the roentgenogram, and little or no rise in temperature with the vasomotor test. The patients considered to have a fair circulation had moderately severe but not hopeless damage to their arterial circulation. They were in an intermediate position between those with slight impairment and those with severe damage. They gave a past history of claudication but no rest pain. There were moderate temperature, color, and trophic changes in the feet. The dorsalis pedis and posterior tibial arteries had lost their pulsation, but it remained in the popliteal artery. The vasomotor test showed only a moderate rise in temperature with vasoconstriction release. Those placed in the group with a good circulation had a competent blood supply to the feet, but showed evidence of arterial damage, such as symptoms of coldness or numbness, calcification of the vessels in the roentgenogram, or slight temperature and color changes. There was always a detectable, though diminished, pulse in either the dorsalis pedis or posterior tibial arteries in these cases. Infection was usually the indication for admission to the hospital since gangrene was only present in sixteen of the sixty-nine cases. There were twenty-one patients in this series who had no detectable damage to the arteries of their feet, either by physical examination, roentgenographic study, or laboratory tests. They were considered to have a normal circulation. Gangrene caused by infection was present in five cases.

Any division into separate categories has the disadvantage of sharply dividing the cases into groups, whereas actually there are gradual gradations of change. There is no way of quantitatively estimating the percentage of circulatory deficit and, therefore, no way to state specifically how much damage has been done.

ANALYSIS OF RESULTS

General.—There were 211 diabetic patients in the group studied who were admitted to the hospital with infected, pregangrenous, or gangrenous lesions of the feet. They created 277 case records, since some had individual or bilateral lesions which required a separate hospital admission. This was considered a distinct case for study, since it presented its own problem. Of these cases, 102 had poor, 85 had fair, 69 had good, and 21 had excellent (or normal) circulation. This, in itself, is informative, for it shows that the majority (67 per cent) of those who enter the hopsital with lesions of the feet already have a serious circulatory defect. This handicaps conservative treatment from the very beginning.

There were 87 men and 124 women in the group. Their average age was 63 years, with extremes from 43 for the youngest to 89 for the oldest. The largest number were in the sixth decade of life. There were nine patients admitted to the hospital in extremis who died and thirteen who refused treatment and left against advice. These should be eliminated.

If this is done, there remain 255 cases who were admitted to the hospital and treated for infection or gangrene of the feet, with forty-one deaths or a surgical mortality of 16 per cent.

TABLE I

255 CASES OF INFECTION OR GANGRENE IN DIABETIC PATIENTS

CIRCULATION	TOTAL CASES	LEG AMPUTATION				FOOT OPERATIONS ATTEMPTED				NO OPERATION	
		PRIMARY	SECONDARY	TOTAL	MORTALITY (%)	CASES	% OF GROUP	SUCCESS	DEATHS	CASES	% OF GROUP
Poor	88	50	14	73%	28	23	26	7 (30%)	12	15	17
Fair	77	18	14	38%	39	35	45	19 (54%)	2	24	31
Good	69	1	9	14.5%	30	47	68	35 (90%)	3	21	30
Normal	21	0	0	0 %	—	17	81	17 (100%)	0	4	19

Table I, which gives the results of treatment, demonstrates the importance of the circulatory factor in the management of these cases. It is expected that improvement in the circulation would diminish the number of leg amputations and increase the successful operations upon the foot. But it is surprising to find that the mortality from leg amputation is no less with a good than with a poor circulation. This is explained by the increased incidence of acute infection as an indication for amputation in the cases with a competent blood supply and illustrates the importance of infection in causing death.

It should be noted that sixty-four, or 25 per cent, of the 255 cases in the series were cured by conservative, nonoperative treatment. They had superficial wounds which were occasionally treated by removing scabs, crusts, slough, or parts of the nail, but none had an operation of sufficient magnitude to require an anesthetic. Such lesions should be considered, for they often develop into a serious gangrene. Or, if they cannot be made to heal, a leg amputation is often the only other alternative. The conservative treatment becomes dangerous if the wound or infection from it extends into the deeper structures of the foot. If this occurs, operative intervention is indicated.

OPERATIONS ON THE FOOT

Diabetic patients with an adequate circulation who have infected or gangrenous lesions of the foot should be cured by a well-executed local operation. Table II shows that this is always true in the normal group, but not invariably so in those classed as having a good circulation. Here infection, spreading along fascial planes despite wide drainage, was always the cause of failure. But this is the exception, so the attempt to save the foot should be made, for leg amputation is usually a needless sacrifice.

Patients with an inadequate circulation often fail to heal operative wounds in the foot. The percentage of success is small, and the hospital

TABLE II

OPERATIONS ON THE FOOT

CIRCULATION	CASES OF FOOT OPERATIONS	PERCENTAGE OF GROUP	DIED AFTER FOOT OPERATION	SECONDARY LEG AMPUTATION	DIED AFTER LEG AMPUTATION	HEALED FOOT WOUND	DAYS TO HEAL	SUCCESS (%)
Poor	23	26	2	14 (61%)	5	7	161	30
Fair	35	45	2	14 (40%)	4	19	64	54
Good	47	68	3	9 (19%)	2	35	55	74
Normal	17	81	0	0	0	17	22	100

TABLE IIA

TOE AMPUTATION

CIRCULATION	CASES OF TOE AMPUTATION	PERCENTAGE OF GROUP	DIED AFTER TOE AMPUTATION	SECONDARY LEG AMPUTATION	DIED AFTER LEG AMPUTATION	HEALED FOOT WOUND	DAYS TO HEAL	SUCCESS (%)
Poor	17	20	1	12 (71%)	3	4	126	23
Fair	29	39	2	13 (45%)	3	14	93	48
Good	34	50	3	6 (18%)	1	25	62	73
Normal	7	33	0	0	0	7	23	100

TABLE IIB

PLANTAR ABSCESS

CIRCULATION	CASES OF PLANTAR ABSCESS	PERCENTAGE OF GROUP	DIED AFTER INCISION	LEG AMPUTATION	DIED AFTER LEG AMPUTATION	HEALED FOOT WOUND	DAYS TO HEAL	SUCCESS (%)
Poor	18	20	0	16 (89%)	6	2	270	11
Fair	19	24	1	15 (79%)	6	3	180	16
Good	24	35	2	9 (37%)	2	13	63	54
Normal	3	14	0	0	0	3	36	100

stay is long. It is important to determine if harm comes from the unsuccessful attempts at foot surgery. It was found that the mortality after toe amputation was 11 per cent; of leg amputation after foot operation, 26 per cent; and of primary leg amputation, 32 per cent. This would indicate a diminished risk after attempted local operation. Moreover, multiple operations on the foot did not increase the mortality rate or diminish the chance of healing; they only prolonged the hospital stay. The real hazard of attempted foot surgery was the introduction of suppuration into the plantar space. This important possibility should be kept in mind when considering an operation on an uninfected foot in a patient with an inadequate circulation. The prospect of success is small and the risk of introducing infection is great, and, therefore, it is best to avoid local surgery.

Plantar abscess was separated in Table IIB for special consideration since it was often a troublesome lesion. It is apparent that, in the poor and fair circulatory groups, the treatment by local incision gives poor results and causes long hospitalization. It is not a satisfactory method of therapy. But it is also seen that the mortality of leg amputation is high, being nearly 40 per cent. This may be subdivided into thirty-two cases treated by primary amputation, with a mortality of 31 per cent, and eight cases treated by secondary amputation, with a mortality of 50 per cent. So, a patient with an inadequate circulation who develops a plantar abscess faces a grave situation which cannot be treated satisfactorily by either local incision or leg amputation. The only other alternative is a two-stage operation with excision of the infected part, followed by leg amputation at a later date.

Cases with an adequate (good or normal) circulation respond more satisfactorily to incision and drainage of a plantar abscess. All of those with a normal circulation and over one-half of those with a good circulation were cured by operations upon the foot.

The impression was gained that one could persist too long in doing multiple operations on these cases. The best results are obtained from wide drainage secured at the first operation. If small secondary pockets occur, they may be opened, but if there is a steady progression of the infection, the prospect of success is slight. Suppuration which extended into the calf was never healed by incision and drainage although this was often attempted.

LEG AMPUTATION

Loss of a limb constitutes a serious threat to the life of a diabetic patient. Our mortality rate from leg amputation was 32 per cent. This was too high and led to an evaluation of the factors that might influence the result. We could find no consistent influence from age, sex, or severity of the diabetes. The competence of the circulation made no difference, for it is seen in Table I that the mortality rate for leg am-

putation in the poor circulatory group is 28 per cent, in the fair group, 39 per cent, and in the good group, 30 per cent. If these figures are correlated with the incidence of infection, it is found that 60 per cent of the poor, 72 per cent of the fair, and 100 per cent of the good circulatory group had acute infection at the time of amputation. This led us to regroup our cases in relation to the presence or absence of acute infection. Fever above 38° C., spreading cellulitis, lymphangitis or pus in the plantar space were considered to be indications of acute infection. Patients with chronically infected lesions were placed in the same group as those who had no infection. It was found that primary leg amputation done in cases *with acute infection* in the foot had a 45 per cent mortality. Primary leg amputation *without acute infection* in the foot had a 12 per cent mortality. In addition, of those with acute infection that survived, 80 per cent had infection of the stump in contrast to 23 per cent in the noninfected group. Because of this, the hospital stay was prolonged.

The type of organism causing the infection did not seem to influence the result, except that *Bacillus welchii* infections were always serious. Delay of the primary amputation with preoperative treatment did not alter either the mortality rate or the incidence infection of the stump. The majority of our cases had closure of the wound of amputation. In those in which the wound was left open, the mortality rate was the same, for, in both, uninvolved fascial planes and devitalized muscle were exposed to infection.

We found that patients having a secondary leg amputation because of failure of operations on the foot had a mortality rate of 26 per cent. This would indicate that local surgical treatment reduces the risk. But the ideal to be achieved is the reduction to the 12 per cent mortality of those who have no acute infection, for this death rate is due to hazards common to any major operation in these patients. This can be done if the acute infection in the foot is eliminated before the leg is amputated. Zierold[1] has stated this principle and has practiced it by removing all infected or devitalized tissue from the foot. After the patient's temperature had remained at a normal level for three days, leg amputation was done as an elective procedure. Zierold reports a reduction in mortality from 50 to 10 per cent by this procedure. McKittrick[2] and others advocate guillotine amputation in the calf under these circumstances, but McKittrick reports a 35 per cent mortality for his guillotine amputations even though he has attained the excellent result of a 13.9 per cent mortality for all of his major amputations.

Recently, to avoid cutting through muscle, we have tried removing the infected foot by the atraumatic method of disarticulation at the subastragaloid or ankle joint. Later, after the infection has subsided, leg amputation is done at a higher level.

CONCLUSIONS

1. Adequate treatment of gangrene in diabetes requires evaluation of the factors of circulation and infection, for upon these rests the type of therapy and the result.

2. Conservative nonoperative treatment of *superficial* lesions is proper in all degrees of circulatory damage so long as the lesion or infection does not extend into the foot. This course is justified by a cure of 25 per cent of our cases by this method. There is often no alternative but leg amputation.

3. Conservative operative treatment on the foot is indicated in cases with an adequate circulation (good or normal). Leg amputation is usually a needless sacrifice. We obtained 90 per cent cures by operations on the foot in these cases. The failure of the first operation does not increase the mortality or reduce the prospect of success of subsequent procedures; it only prolongs the hospital stay.

4. Patients with an inadequate circulation (fair or poor) who have ischemic gangrene should not be treated conservatively, for delay or local operations may permit infection of the foot. A primary leg amputation is indicated.

5. Patients with inadequate circulation who have infection in the foot may be treated by local operation without increased risk, but the results are poor, for few heal the wound even after a prolonged hospital stay.

6. Patients with acute infection in the foot should never have a primary leg amputation, for the mortality rate was 45 per cent in our series. In contrast, patients without acute infection had a 12 per cent mortality from leg amputation. We believe that patients with an inadequate circulation who have an acute infection are best treated by removal of the infected foot, followed by leg amputation at a later date.

REFERENCES

1. Zierold, A. A.: Gangrene of the Extremity in the Diabetic, Ann. Surg. **110**: 723, 1939.
2. McKittrick, L. S.: Diabetic Gangrene, Arch. Surg. **40**: 352, 1940.

GASTRIC RESECTION WITH REMOVAL OF THE FUNDUS IN THE TREATMENT OF DUODENAL ULCER

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THE modern medical treatment of duodenal ulcer is so effective that only the exceptional case requires surgical therapy. In contrast with the situation twenty years ago, when over 50 per cent of such patients came to surgery, now not more than 8 to 10 per cent require surgical treatment.[16] For the treatment of these patients there is a wide choice of operations available to the surgeon. It is not the purpose of this paper to enter into a discussion of conservative versus radical surgery in the treatment of duodenal ulcer but rather to discuss a procedure which aims at a reduction in the total amount of hydrochloric acid secreted.

We have two reasons for utilizing fundusectomy. First, we have been dissatisfied with the results obtained by some of the other accepted methods of resection. In the surgical management of duodenal ulcer in the Peter Bent Brigham Hospital we have attempted to follow the physiologic implications laid down as the result of experimentation on this problem. In our opinion the Horsley modification of the Billroth I type of operation seemed to answer best the experimental requirements. It provides for resection of the ulcer-bearing area and reanastomosis of the remaining stomach to the duodenum, which has a higher tissue resistance to gastric juice than the jejunum; it gives a patulous pylorus, so essential in avoiding recurrent ulceration from a mechanical cause; and, in addition, it permits a certain amount of intragastric regurgitation of alkaline duodenal juices. But after clinical trial, when approximately 50 per cent of the cases followed for five years developed recurrent difficulty, it was abandoned.

From clinical and experimental evidence repeatedly presented, the important role played by the acid factor in the etiology of duodenal and gastrojejunal ulceration must be acknowledged. The weakness of Billroth II types of resection is that sufficient acid-bearing tissue is not removed. Even in so-called radical resection of the Billroth II type, when three-quarters or more of the stomach is removed, it is customary to carry the resection high on the lesser curvature and to leave a sufficient amount of greater curvature to facilitate gastrojejunal anastomosis. Apparently fear of a gastric ulcer developing in this location after resection prompts this wide removal of lesser curvature. Clinically, however, recurrent ulceration occurs almost invariably in the jejunum

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or about the stoma and is uncommon on the lesser curvature after resection for duodenal ulcer. It is also infrequent after gastroenterostomy, as shown by Ginzburg and Mage. They found, in a study of 86 specimens resected because of the failure of posterior gastroenterostomy, that lesser curvature ulcers developed in only six instances. In each case posterior gastroenterostomy had been performed originally for duodenal ulcer. Not only do marginal or jejunal ulcers occur after conservative surgical procedures, but they are not infrequent after the Billroth II types of resection.[10] A five-year follow-up, including roentgenologic examination, of a group of selected cases of intractable duodenal ulcer having had resection would probably show a distressingly high percentage with recurrent difficulties. The incidence of recurrent ulceration after resection may be partially explained by the fact that various amounts of fundus, rich in surface area of acid-secreting tissue, have been retained, although most of the lesser curvature, low in surface area of acid-secreting tissue, has been resected.

Second, the clinical results and experimental evidence imply that fundusectomy is sound. A number of years ago Connell[3, 4] proposed diminishing the hydrochloric acid secretion in patients with intractable duodenal ulcer by means of partial fundusectomy. He has since reported satisfactory results with the use of this procedure in the treatment of complicated jejunal ulcerations as well.[6]

Accumulated experimental evidence, however, has perhaps retarded the widespread use of fundusectomy, since it has been repeatedly demonstrated that the acid value by gastric analysis returns to normal within a period of a few months, depending upon the amount of fundus removed.[8, 12, 14, 15] As Mann[5] and others have pointed out, however, if permanent clinical results are to follow fundusectomy, it must be on the basis of actual reduction of the amount of gastric juice and not of any change in the degree of acidity as shown by gastric analysis.

That the volume of acid secreted is markedly decreased may be assumed from comparing a cross section of the stomach of a normal dog with that of one in which the fundus has been resected (Fig. 1). In dogs, despite removal of a large amount of the fundus, the stomach eventually returns to approximately normal size and capacity. The effect of removal of the fundus can more easily be appreciated after fixation and sectioning of the stomachs at corresponding levels. Normally, the region of the fundus along the greater curvature presents a great duplication of thick folds, providing a large surface area of acid-secreting tissue, but after fundusectomy a section at a corresponding level shows an absence of folds. Although the acid values by gastric analysis would appear the same, the volume of acid secreted would obviously be tremendously decreased in the second specimen. After fundusectomy the alkaline juices would be sufficient to combat the decreased volume of gastric juice, thereby preventing recurrent ulceration. Confirmation of this is suggested by the investigations of Fauley and

Ivy, who performed fundusectomy in animals and followed it subsequently by the Mann-Williamson operation. They found that, although the free acid and total acid values returned to normal within a period of six to eight months, the quantity of gastric juice that could be aspirated in response to injection of histamine was substantially less than in nonfundusectomized Mann-Williamson dogs and slightly less than in normal control animals. Furthermore, they found that fundusectomy, combined with an easily assimilable diet, protected the Mann-Williamson animals against ulceration for the two years during which the animals were observed. This protection was not universally effective without the special diet, but it seemed to indicate a decrease in the quantity of acid available for prolonged irritation of the jejunum. Not only do the experiments of Fauley and Ivy indicate the possible usefulness of fundusectomy in the treatment of jejunal ulcer, but they serve to emphasize the need for a strict dietary regimen in patients after operation.

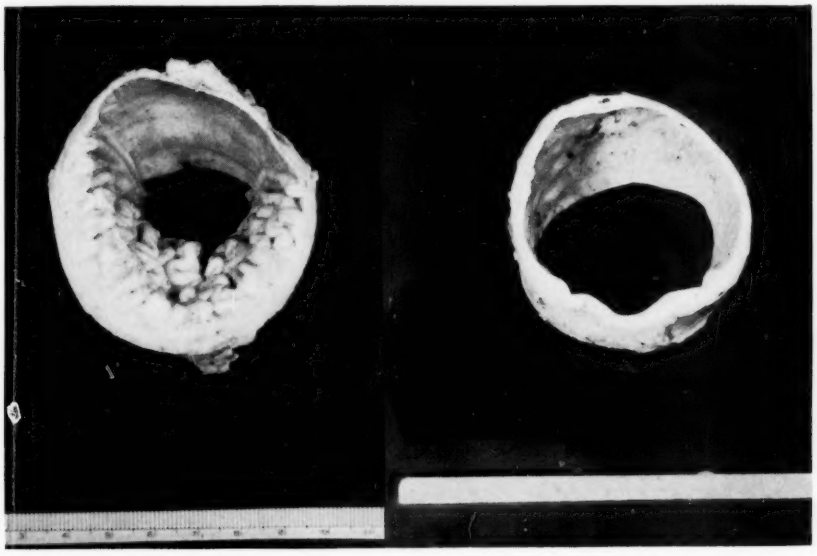

Fig. 1.—*A*, A transverse block taken through the midfundus of stomach of a normal dog. Note smooth *magenstrasse* of inner curvature and the immense reduplication of mucous membrane over greater curvature. *B*, Transverse block through the midfundus of stomach of a dog after fundusectomy. Rugae are almost totally lacking. (From Seeley and Zollinger: Courtesy of Surg. Gynec. & Obst. **61**: 155-161, 1935.)

After weighing the experimental and clinical evidence for fundusectomy, we carried out, in addition to resection of the stomach by the Polya method, a removal of varying amounts of the fundus (Fig. 2). Resection of the antrum, especially in severe cases of jejunal ulceration after gastroenterostomy, seemed desirable in the belief not so much that it would reduce the secretory capacity of the stomach as that it would provide a patulous stoma. In addition to fundusectomy a departure from the radical type of Polya resection was decided upon, in that the lesser curvature was not to be divided high but in the neighborhood of

the incisura angularis. This would insure a longer tube of stomach along the lesser curvature, would provide a more satisfactory postoperative gastric capacity, and would facilitate gastrojejunal anastomosis. The anastomosis could be easily carried out in the immediate field of operation with adequate room and exposure for the meticulous technical steps associated with closure of the upper and lower angles of the stoma. The obvious difficulty that suggested itself was the danger associated with the approximation of two suture lines at the lower end of the gastrojejunal anastomosis especially, when the blood supply of the remaining stomach would be dependent only on the left gastric artery (Fig. 2). Injection of the left gastric artery in a stomach removed at post mortem, using a mixture utilized by Schlesinger, clearly demonstrated the rich blood supplied by the left gastric artery (Fig. 3). Although the blood supply could be shown to be adequate, even in the region where the two suture lines would be approximated, the technical details of such a procedure were first tested experimentally in animals. Since we carried out these experiments, Wangensteen has reported extensive removal of the acid-bearing tissue, including the fundus. He did not hesitate to do a gastroenterostomy at various levels along the suture line and had no difficulty from impaired blood supply.

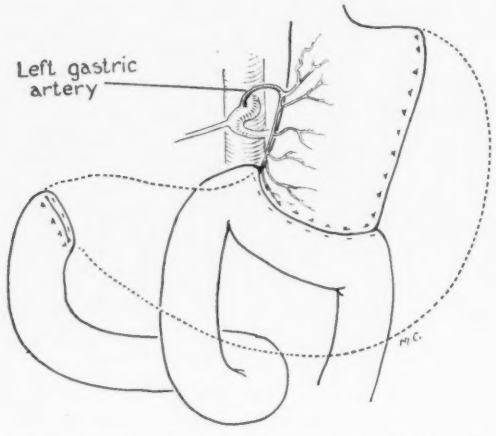

Fig. 2.—Schematic drawing, illustrating Polya resection combined with fundusectomy. Note the amount of lesser curvature retained.

The following experiments were carried out. The lesser curvature was divided between medium-sized Payr clamps about the incisura angularis in the majority of instances. The fundus was then resected, leaving only a narrow tube along the lesser curvature (Fig. 2). Following resection, an anastomosis was made between the open end of the stomach and the upper jejunum. It was found that the blood supply was adequate and that approximation of the two suture lines at the lower angle of the anastomosis could be carried out with safety. Results were the same whether the proximal jejunum was anastomosed to the lesser or to the greater curvature. Four dogs survived this procedure and were allowed to live from six to thirteen months.

At the time of sacrifice, none of the animals showed evidence of jejunal ulceration. In the first animal the lesser curvature was divided so high that only a short tube of stomach remained. In spite of hypertrophy of the gastric remnant, the stomach was apparently insufficient. The animal could retain little food and was emaciated when sacrificed thirteen months after operation. The remaining three animals, in which the lesser curvature had been divided about the incisura angularis, remained in excellent condition and showed no essential variation in weight. There was considerable hypertrophy and dilatation of the stomach at the time of sacrifice (Fig. 4). Injection of the left gastric artery demonstrated a liberal and adequate blood supply to the stomach (Fig. 4). Gastric analyses were not carried out in these animals because experimental data have been accumulated to indicate that the gastric analyses had returned to normal by the time of sacrifice. The volume of acid secreted, however, must have been materially decreased.

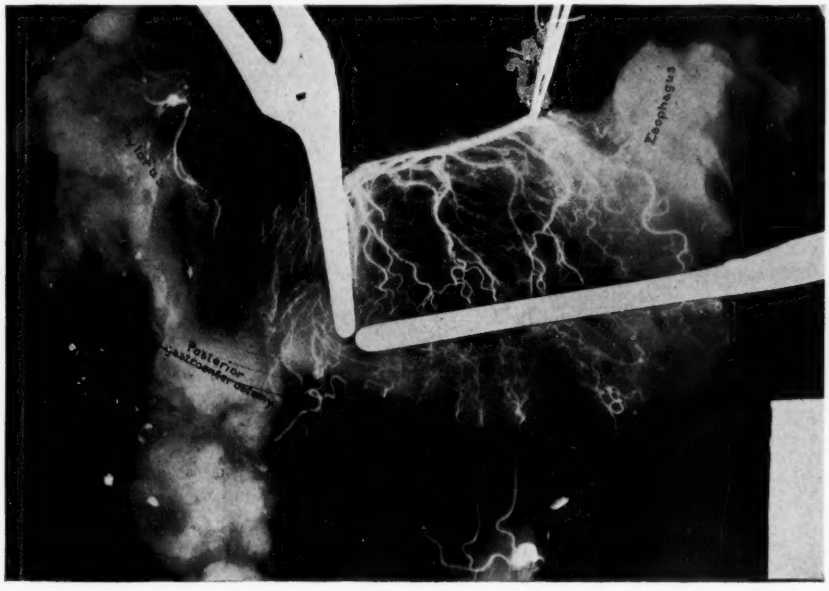

Fig. 3.—Injection of opaque material into left gastric artery of post-mortem specimen, illustrating the adequacy of the blood supply. Payr clamps outline the amount of stomach retained.

Before attempting fundusectomy, the surgeon should be familiar with the extent and distribution of the acid-secreting cells of the stomach to insure removal of a sufficient amount of acid-bearing tissue. Berger's study shows that there is a zone in the region of the cardia where the ratio of acid-bearing cells is about 50 per cent. This is in contrast to 100 per cent for a large area extending from the cardia down to the region of the incisura angularis and over to the junction of the body and antrum. He found a limited transition zone in the region of the incisura angularis where the incidence of acid-bearing cells is 75 per cent. In view of the large folds of mucosa along the greater curvature

in the region of the body and fundus it is obvious that here is a chief area of acid-secreting tissue. This is shown schematically by the wavy lines in the drawing in the 100 per cent zone of parietal cells (Fig. 5). In order that sufficient acid-bearing tissue may be removed, the resection must extend well up toward the esophagus along the greater curvature.

Gastric resection with removal of a large amount of the acid-bearing tissue by means of fundusectomy and with restoration of gastric con-

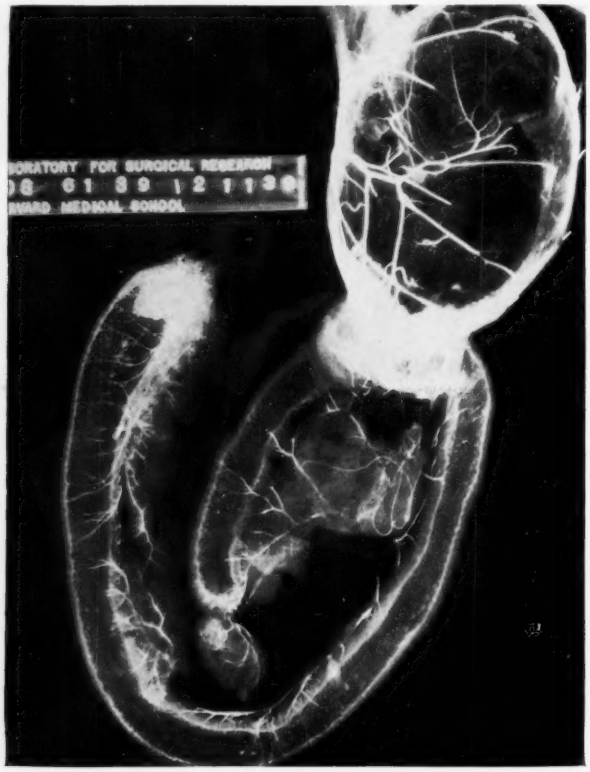

Fig. 4.—Injected specimen of stomach of a dog six months after resection with fundusectomy. The left gastric artery has been injected with opaque material. The stomach has satisfactory capacity.

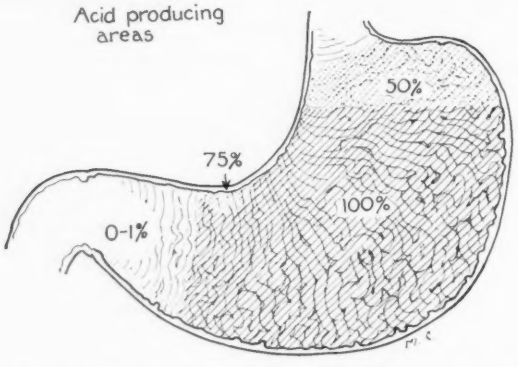

Fig. 5.—Schematic drawing of acid-bearing area, illustrating the reduplication of folds along the greater curvature and the percentage of acid-bearing cells at various levels (Berger).

tinuity by a gastrojejunostomy of the Polya type to a long tube of lesser curvature has been performed in the following manner on two patients: Under ether anesthesia the abdomen was opened through a high, left, paramedian incision. After the ligation of the blood supply to the region of the pylorus, the pylorus was divided and the duodenum was closed. The blood supply of the lesser curvature was then carefully ligated up to the incisura angularis. The blood supply of the greater curvature was next ligated high on the fundus, unless adhesions between the stomach and spleen interfered (Fig. 6). As Wangensteen has pointed out, it may be difficult to mobilize the fundus entirely because of a short gastrosplenic omentum. Usually, however, this is not a particularly difficult problem. The left gastric artery now remained as

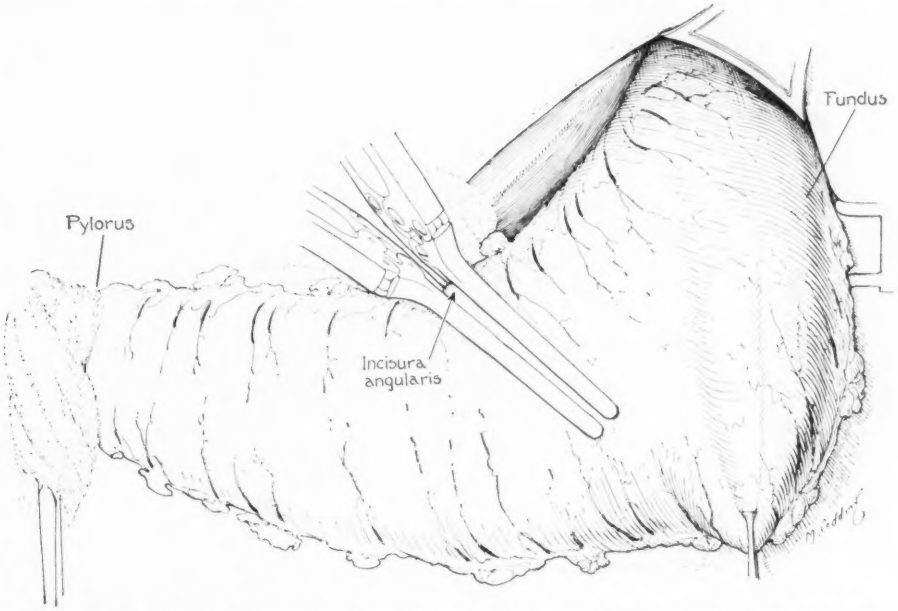

Fig. 6.—The duodenum has been divided and closed. The blood supply of the stomach has been divided to the incisura angularis and high on the fundus. Medium-sized Payr clamps are applied at the incisura angularis in preparation for division of the lesser curvature.

the source of the blood supply. An area on the lesser curvature about the incisura angularis and one high on the fundus at a selected level were freed of fat in preparation for the application of clamps. A pair of medium-sized Payr clamps of sufficient size to permit the subsequent stoma to admit approximately three fingers were applied at the point prepared on the lesser curvature (Fig. 6). The tissue between the clamps was divided with the cautery and the Payr clamp toward the pylorus was reflected downward (Fig. 7). Two long Payr clamps were applied close to the tip of the remaining Payr clamp and as high on the fundus as it had been prepared (Fig. 7). As the first large clamp is applied, the surgeon should assure himself that the stomach is not rotated and that sufficient stomach remains so that, when the contents of the large Payr clamp are sutured and inverted, there is a satisfactory

lumen of the stomach along the lesser curvature. The use of a DePetz sewing clamp, as advocated by Wangensteen, should facilitate the closure of the newly made greater curvature. A cautery was again used to divide the contents of the large Payr clamps. A running, continuous silk suture on a milliner's needle was started near the toe of the clamp and was passed beneath the clamp to approximate the gastric walls and

Fig. 7.—The lesser curvature has been divided. A pair of large Payr clamps are applied in preparation for resection of the fundus. A sufficient lumen of the stomach along the lesser curvature must be assured before the large clamps are finally locked.

to control the blood supply (Fig. 8). This suture was carried up to the toe of the smaller Payr clamp and tied. The crushed contents of the large Payr clamp may be excised and additional sutures taken, if necessary, to approximate more accurately the cut margin of the gastric wall and to control any bleeding points. This suture line was buried by a second layer of interrupted sutures of the Halsted mattress type (Fig. 9). These interrupted sutures were also carried up to the small Payr clamp.

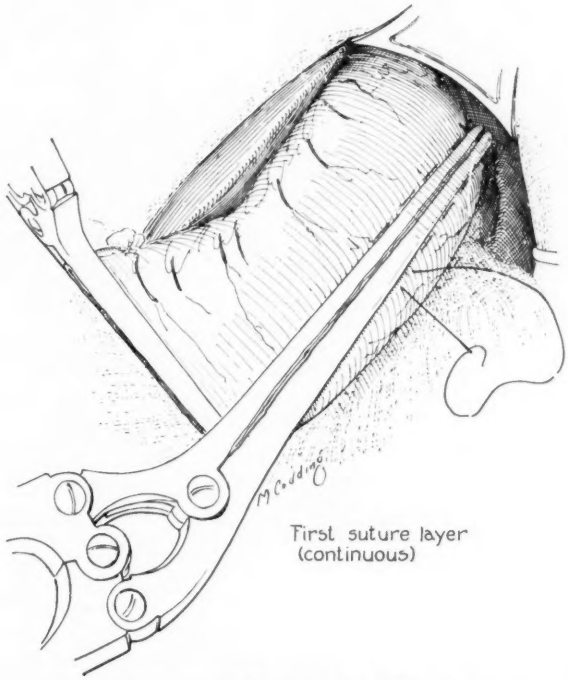

Fig. 8.—The contents of the large Payr clamp are approximated with a continuous silk suture. The crushed contents of the clamp are excised.

Each of the two patients in whom this operation was carried out had had a previous gastroenterostomy with a resultant jejunal ulcer, so that it was necessary to close the opening in the jejunum and to select a site distal to the ulcerated area for the new gastrojejunal stoma. A routine gastrojejunal anastomosis of the Polya type was performed (Fig. 10). By dividing the stomach low on the lesser curvature, the gastrojejunal anastomosis can be done in the immediate operative field. There has been no particular difficulty experienced in closing the inferior angle of the stoma where it meets the suture line of the fundusectomy. The jejunum, however, should preferably be anchored with interrupted Halsted sutures slightly up over the lesser curvature and for a short distance at the inferior angle to avoid tension on the initial sutures about the angles of the anastomosis (Fig. 11). The mesocolon was then anchored up above the gastrojejunal anastomosis. In both of the patients in whom this technique was followed a stoma which would admit three fingers was obtained.

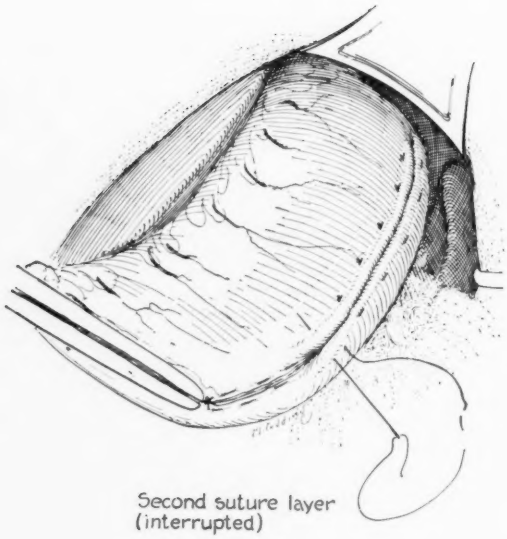

Fig. 9.

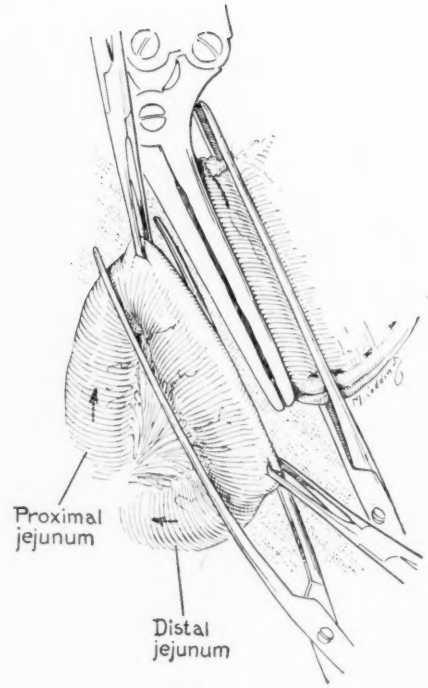

Fig. 10.

Fig. 9.—A final serosal layer of interrupted silk mattress sutures is taken to cover the initial suture line.

Fig. 10.—The jejunum is anastomosed to the entire open end of the stomach. The stoma should admit approximately three fingers.

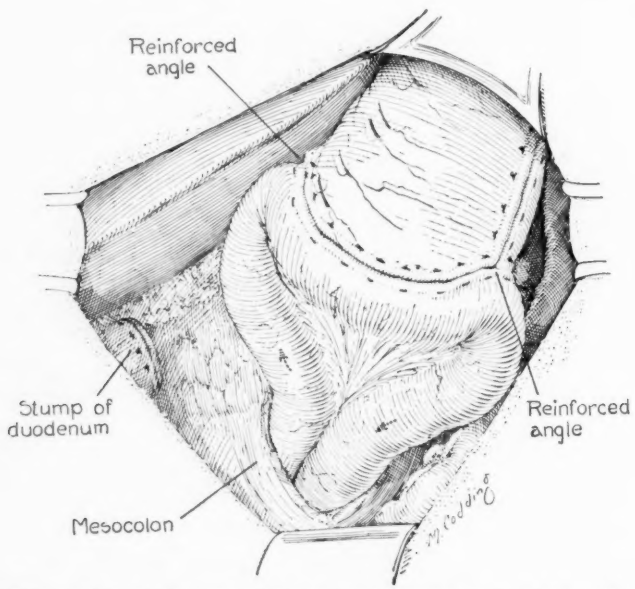

Fig. 11.—The angles of the gastrojejunal anastomosis are reinforced with several additional interrupted silk sutures. The mesocolon is anchored to the stomach above the anastomosis.

The two patients selected for this procedure had jejunal ulceration after posterior gastroenterostomy for duodenal ulcer. Their symptoms were not relieved by hospitalization and adequate medical treatment.

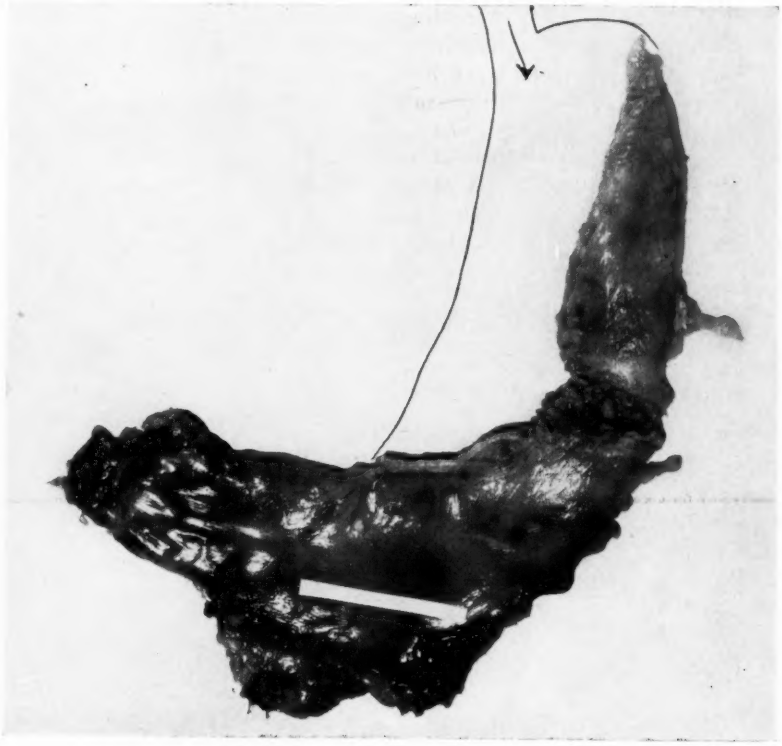

Fig. 12.—A specimen of Case 1, illustrating the extensive removal of fundus and the amount of stomach retained along the lesser curvature.

REPORT OF CASES

CASE 1.—A 43-year-old Jewish bartender had ulcer symptoms intermittently over a period of twenty-five years. In 1921 a posterior gastroenterostomy was performed elsewhere with relief of symptoms for six months. In 1923 another gastric operation was performed, the details of which are lacking. Following the second gastric operation the patient was free of symptoms for approximately ten years. However, for six years prior to his entry on the Medical Service of the Peter Bent Brigham Hospital, May 12, 1939, he had recurrent symptoms which gradually increased in severity. He had a proved jejunal ulcer which failed to respond to medical treatment. He was kept on a strict Sippy regimen for thirty-five days with a constant cremalin drip for six days. Because of continued distress, he was given eight roentgen-ray treatments in an effort to reduce the gastric acidity. He was then discharged from the hospital. He gained ten pounds in weight. Although he improved after the x-ray therapy, he was not completely relieved of his symptoms and accordingly he entered the Surgical Service on July 21, 1939. A gastric analysis on the Medical Service had shown free acid of 65 and a total acid as high as 92, but following the x-ray therapy the acid values by gastric analysis were substantially decreased. On July 26, 1939, an exploratory operation was performed. This showed a healed duodenal ulcer and a jejunal ulcer. The operation previously described was performed with closure of the jejunum at the site of the ulcer. A point was selected

for the anastomosis about 12 cm. distal. The specimen measured 30 cm. along the greater curvature; 1.5 cm. of duodenum were included in this resection (Fig. 12).

The patient had an uneventful postoperative course. He occasionally vomited a small amount of bile, especially at night, but otherwise all symptoms were relieved. His economic situation, which did not permit an adequate diet, was thought to be responsible for this complaint. Accordingly he was brought back to the hospital for regulation of his diet and for further investigation. He now has work which provides a living wage and has since been symptom free. It is six months since his operation was performed. X-ray examination six months after operation showed a tubular stomach, 8 cm. in length and 6 cm. wide (Fig. 13). The stomach emptied rapidly and there was no evidence of tenderness or crater about the stoma. At the time of operation, silver clips (Cushing) were placed along the greater curvature, about the stoma, and at the site of the previous jejunal ulcer. These, it was hoped, might proved of value in estimating the amount of subsequent hypertrophy and dilatation of the gastric tube at roentgenologic examination.

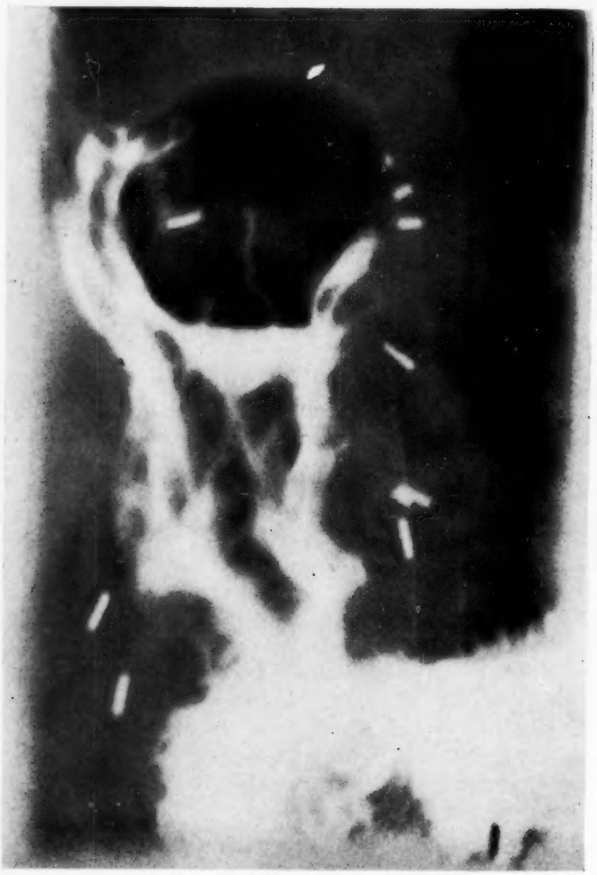

Fig. 13.—Barium study of Case 1, six months after operation, showing a small tube of lesser curvature. The metal clips outline the extent of the fundusectomy and the angles of the gastrojejunal anastomosis.

CASE 2.—A 50-year-old laborer, originally from the British West Indies, entered the Medical Service of the Peter Bent Brigham Hospital, Dec. 8, 1939, for his seventh hospital admission. He complained of severe epigastric distress and anorexia. In 1924 a posterior gastroenterostomy was performed elsewhere for duodenal ulcer with relief of symptoms for two years. Since that time he has been treated in the Out-Patient Department because of recurrent symptoms. Five of his hospital ad-

missions were for pain associated with jejunal ulcer, and one was for a severe hemorrhage with a fall in the red blood count to two million. He has had previous tarry stools and on various occasions had vomited coffee-ground material. A jejunal ulcer was proved by x-ray in 1930 and by subsequent examinations. During two weeks of treatment on the Medical Service he showed only partial improvement. It was felt that he was a severe case which required radical resection. Gastric analysis,

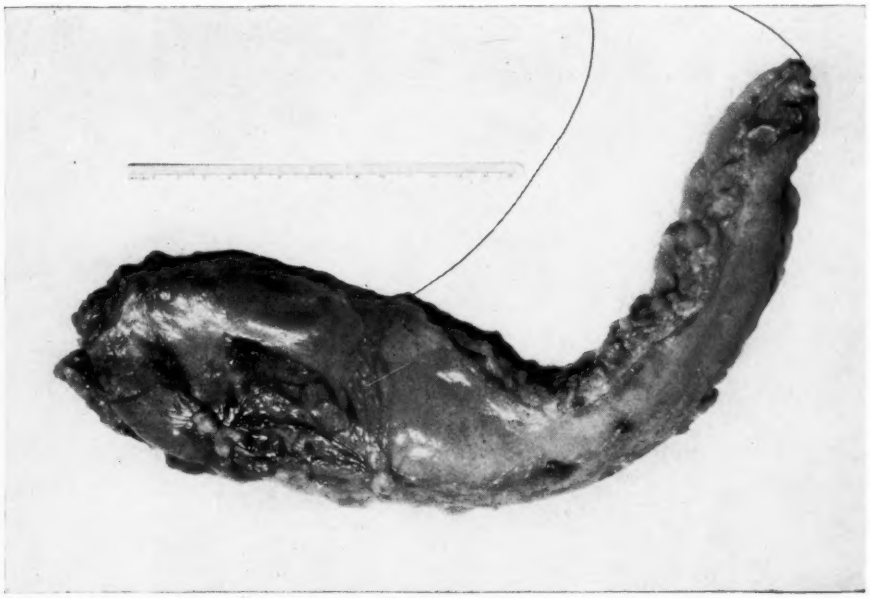

Fig. 14.—Specimen of Case 2, showing the amount of stomach resected.

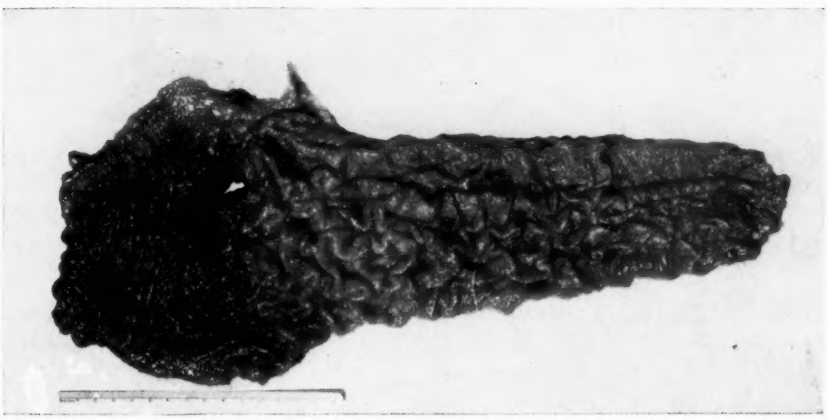

Fig. 15.—Specimen of Case 2 opened, showing the small stoma of the previous gastroenterostomy as well as the large folds of acid-bearing tissue removed by fundusectomy.

from time to time, showed a free acid as high as 70, which went as high as 105 after histamine. As much as 150 c.c. of acid could be aspirated after histamine. On Dec. 20, 1939, a radical resection with fundusectomy was carried out. In this patient the resection was not carried quite as high on the fundus as described in Case 1. However, the stomach was large so that the resected specimen measured 37 cm. along the greater curvature (Fig. 14). The specimen, when opened, showed that the resection had apparently been carried high enough on the greater curvature to extend above the large rugae (Fig. 15). At that time a jejunal ulcer was found, and the

jejunum was closed at this point. The site for anastomosis was selected about 12 cm. beyond the point of jejunal ulceration. The postoperative course was uneventful.

Postoperative x-rays showed that the remaining portion of the stomach was funnel shaped, measuring 13 cm. in length and 9 cm. in width at the upper end (Fig. 16). Barium emptied rapidly through the stoma. Although the period since operation has been short, this patient has been entirely symptom free and has a gastric capacity greater than the first patient.

Fig. 16.—Barium study of Case 2, one month after operation, showing a larger gastric capacity than Case 1.

The gastric secretion in both patients after operation is consistent with the amount of fundus removed and with experimental findings. It is difficult though to obtain an accurate estimation of the volume response by gastric analysis because the stomach empties so rapidly in these patients. We are not so much interested in the return of acid values, because we expect that these patients may develop a relatively normal gastric analysis. However, these patients will be checked repeatedly for the volume response to histamine by the continuous aspiration method as advocated by Bloomfield and Polland. Repeated analyses by their careful method should give information as to whether or not there will be a subsequent increase in the volume, which might approach the preoperative analyses. Furthermore, it is realized that neither one of these patients has been studied long enough after operation for definite con-

clusions to be drawn. Such an examination, to be of any value, must be done at least a year after operation. Wangensteen has reported that the patients in whom he has carried out a similar radical excision of the fundus showed no free hydrochloric acid on a fasting stomach after an alcohol test meal, and several months after operation three patients had no free hydrochloric acid even after histamine. The one patient who had symptoms after operation showed free hydrochloric acid on a fasting stomach. In this particular patient the excision of the fundus beyond the insertion of the esophagus was omitted.

Sufficient data are not available yet to determine the actual efficacy of fundusectomy, either with or without short-circuiting procedures or resection. The clinical and experimental reports, however, indicate that removal of the fundus might be considered in the severe case of duodenal ulcer or recurrent ulceration following previous surgical procedures. The final evaluation of any operation for ulcer cannot be determined until a sufficient number of cases has been followed, with roentgenologic examinations, for a period of at least five years.

CONCLUSIONS

Experiences in the use of extensive fundusectomy, combined with the Polya type of resection, in the treatment of jejunal ulcer following gastroenterostomy are reported.

REFERENCES

1. Berger, Edmund H.: The Distribution of Parietal Cells in the Stomach, Am. J. Anat. **54**: 87, 1934.
2. Bloomfield, Arthur L., and Polland, W. Scott: Gastric Anacidity—Its Relations to Disease, New York, 1933, The Macmillan Co.
3. Connell, F. G.: Fundusectomy, Surg., Gynec. & Obst. **53**: 750, 1931.
4. Connell, F. G.: Resection of Fundus of Stomach for Peptic Ulcer, Ann. Surg. **96**: 200, 1932.
5. Connell, F. G.: Partial Gastric Fundusectomy in Treatment of Peptic Ulcer, Surg., Gynec. & Obst. **59**: 786, 1934.
6. Connell, F. G.: The Problem of Intractable Peptic Ulcer, Surg., Gynec. & Obst. **69**: 287, 1939.
7. Cutler, Elliott C., and Zollinger, Robert: Atlas of Surgical Operations, New York, 1939, The Macmillan Co.
8. Fauley, G. B., and Ivy, A. C.: The Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy, Surg., Gynec. & Obst. **63**: 717, 1936.
9. Ginzburg, Leon, and Mage, Sigmund: Failures Following Gastro-Enterostomy for Gastroduodenal Ulcer, Surg., Gynec. & Obst. **67**: 788, 1938.
10. Lahey, Frank H., and Marshall, Samuel F.: Surgical Treatment of Peptic Ulcer Based Upon 130 Subtotal Gastrectomies for Peptic Ulcer, New England J. Med. **217**: 933, 1937.
11. Schlesinger, M. J.: Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, Am. Heart J. **15**: 528, 1938.
12. Seeley, H., and Zollinger, R.: Fundusectomy in the Treatment of Peptic Ulcer, Surg., Gynec. & Obst. **61**: 155, 1935.
13. Wangensteen, O. H.: Aseptic Gastric Resection: I. A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus, Stomach, Small or Large Intestine); II. Including Preliminary Description of Subtotal Excision of the Acid Secreting Area for Ulcer, Surg., Gynec. & Obst. **70**: 59, 1940.
14. Watson, J. R.: Effect of Fundusectomy on the Acidity of the Gastric and Duodenal Content, Arch. Surg. **31**: 1, 1935.
15. Zilocchi, E., and Calvi, P. G.: Ricerche Sperimentali sul Chimismo Gastrico dopo Resizione del Fondo dello Stomaco, Arch. per le sc. med. **67**: 153, 1939.
16. Zollinger, R.: The Surgical Aspects of Peptic Ulcer, Rhode Island M. J. **21**: 113, 1938.

RIGHT COLECTOMY IN ONE STAGE

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WE HAVE had 27 cases of right colectomy at the University of California Hospital during the last ten years. Though this is far from a large number, we believe that something may be gained by a careful analysis and study of these cases. In addition, 14 patients had lesions for which palliative surgery alone could be done, so that the operability of all lesions of the right colon was 66 per cent.

The subject of the value of right colectomy in one stage as opposed to that in two stages is as controversial now as it was years ago. Each procedure has certain advantages and it certainly is not our idea to recommend, dogmatically, that all patients be operated upon in one stage. As in other types of surgery, patients should be selected carefully for each procedure. In our hands the mortality rate of the two types of operation has been approximately the same. We realize, however, that one additional death in either group would make the mortality reading entirely different.

Advantages of the one-stage operation are that the technical procedure is easier, hospitalization is shorter, thereby reducing the cost of medical care, and only one anesthetic need be administered instead of two. We believe that an earlier recognition of lesions in the right colon, which is the most significant factor influencing the mortality rate, longer preparation before operation, and greater attention to technique will permit more patients to be operated upon by the one-stage procedure, with a lower mortality, than is the case at present.

In the one-stage procedure it is essential that the bowel be clean and decompressed and the body fluids and chemistry be up to normal. The preoperative care should be continued long enough to permit a study of the function of the liver and kidneys, to build up the blood by transfusion, to decompress the bowel by continuous suction through the stomach, and to wash out the lower bowel by the means of enemas and the giving of epsom salts. These procedures are followed by the use of lead and opium pills for two days. This regime, of course, is not applicable if the patient has an acute obstruction.

Adequate exposure is of first importance and we have found the Hoag[1] incision to be a great improvement over the rectus incision. By its use, mechanical retraction becomes unnecessary, thus lessening trauma to the wound and allowing greater protection to its edges.

The right colon is mobilized in the usual manner by cutting the lateral peritoneum, and the right colon and terminal ileum are freed

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of their blood supply, taking with them the lymphatic area involved. The mobilization, with freeing of the bowel, is continued to the point selected for transection. Before the bowel is cut, the retroperitoneal space is closed as completely as possible. The ease of this closure varies considerably in different patients, but it can be accomplished more readily through the transverse approach mentioned above.[1] At

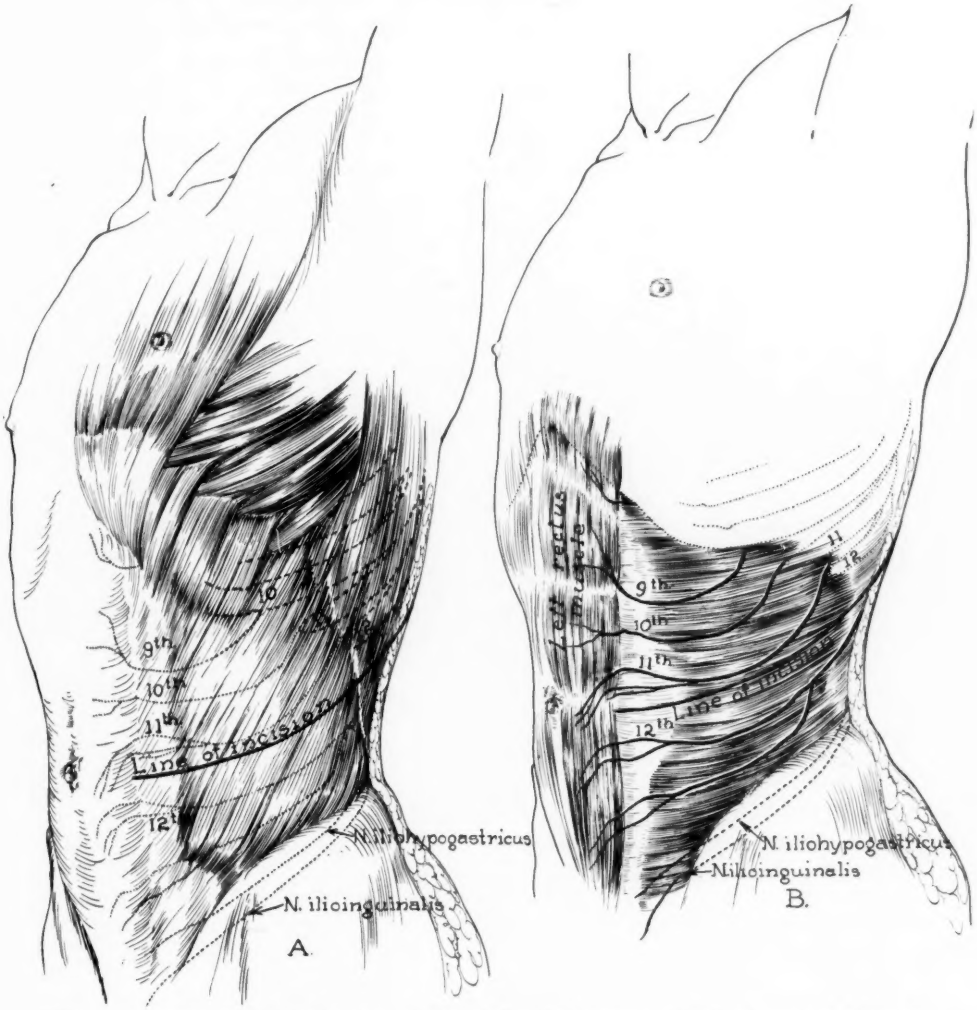

Fig. 1.—Course and distribution of the abdominal nerves. Line of pericostal-transabdominal incision between eleventh and twelfth nerves.

this point, the operation can be completed as a Mikulicz procedure, as advocated by many surgeons, if it seems desirable. If the operation is continued, the flow of intestinal contents in the loop to be resected is prevented by the application of a broad rubber band (Fig. 2). We feel that this causes less trauma to the bowel and the blood supply than clamps do. The bowel is transected between clamps by the electrosurgical unit and the ends of the cut bowel are turned in with catgut

sutures and reinforced with Halsted mattress sutures of silk. During this procedure the wound and abdomen have been packed off carefully so as to prevent the slightest contamination. The ileum and transverse colon are approximated and held in place by traction sutures for a side-to-side anastomosis. We feel that this is the safest anastomosis because the poor blood supply of the transverse colon can thus be supplemented by collateral circulation from the adequate blood supply of the ileum. The abdominal cavity and wound are further isolated by more abdominal packs. The first posterior row of sutures (interrupted silk) is laid, then tied and cut (Fig. 2). The anterior Halsted mattress sutures are laid, retracted over the stay sutures and covered with moistened packs to prevent contamination. The bowel is opened with the electrosurgical unit (Fig. 2) by coagulation and cutting so that there is no bleeding of the cut edges—one of the main sources

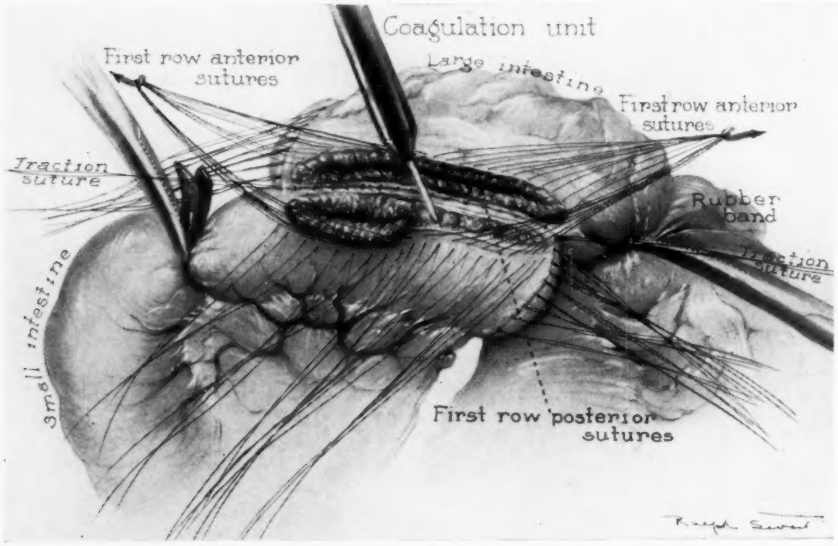

Fig. 2.—Technique of right colectomy. (From Hoag, Carl L.: A New Approach to Resection of Cancer of the Colonic Flexures, California and West Med. 45: 148, 1936.

both of local contamination of the bowel at the site of anastomosis and of soiling of the abdominal cavity. If the machine is adjusted correctly there should be no free blood on the edges of the wound. The idea of using the electrosurgical unit is not original with us, but it seems to us that this feature has not been emphasized strongly enough.

The second posterior row of sutures (catgut), through the entire posterior layer, is then placed and continued anteriorly to catch just the mucosa and submucosa. This row of sutures is laid entirely with instruments. At this point in the operation, both the superficial packs and the gloves are changed so that another opportunity for contamination is eliminated. At this stage the anterior sutures are drawn tight and tied. A second row of Lembert sutures (silk) is placed

anteriorly and tied. The anastomosis is then covered with omentum. Gloves and drapes are changed again before closure of the abdomen is begun. The abdomen is closed without drainage. Enterostomy proximal to the anastomosis is not performed.

In our series of 27 colectomies, 23 were done for carcinoma, with 3 deaths; 2 were done for tuberculosis, 1 for polyps of the ascending colon and 1 for cicatrizing enteritis, with no deaths. Eight were done in two stages, with 1 death, a mortality of 12.5 per cent; 18 were done in one stage with 2 deaths, a mortality of 11.1 per cent; 1 was done as a Mikulicz procedure, with recovery.

The ages of our patients varied from 30 to 74 years, the largest number being between the ages of 60 and 70 years. There were 14 women and 9 men in the series.

Of the 4 patients with lesions other than carcinoma, none has died. Of the 23 with carcinoma, 14 are still alive (Table I) and 9 have died. Three died following surgery. Of the other 6, 1 lived for two years and four months after operation, 2 lived for thirteen months, 1 for eleven months, 1 for nine months, and 1 for five months; all 6 died of metastases. Of the 3 patients who died after operation, 1, a man 52 years old, had uremia following a complete anuria after the second stage of the operation. No injury to the kidneys or ureters was found at autopsy; the anastomosis was intact. One woman, 61 years of age, died as a result of gangrene of a portion of the small bowel. The tumor was attached to the small bowel and mesentery and apparently the blood supply had been injured to the extent of producing gangrene.

TABLE I

CARCINOMA PATIENTS LIVING AND WELL AFTER RIGHT COLECTOMY

LESS THAN 1 YR.	1-2 YR.	2-3 YR.	3-4 YR.	5-6 YR.	6 YR.	TOTAL
7	2	1	1	2	1	14

In many clinics this resection would not have been attempted. At autopsy the suture line was intact. One man, 47 years of age, died on his seventy-first day after operation from abscess of the right lung and empyema. At autopsy the abdomen appeared to be normal.

SUMMARY

Twenty-seven cases of right colectomy, with three deaths, are reported. Longer preparation before operation and more careful surgical technique will save more of these patients from death by peritonitis. In our opinion, the use of the electrocoagulation unit is an added factor of safety.

REFERENCE

1. Hoag, Carl L.: A New Approach to Resection of Cancer of the Colonic Flexures, California & West. Med. **45**: 148, 1936.

PAINFUL SCARS

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FORTUNATELY only a small proportion of cutaneous scars resulting from surgical and accidental wounds remain painful or tender. However, occasional cases are seen in which painful scars are not only annoying to the patient, but may be sufficiently disabling to demand treatment. That excision of the entire scar will usually relieve the symptoms has been well established. Less is known about the cause of the pain, and the fact that only a small area on the scar may be responsible for the symptoms has not been emphasized.

Quain and Eggers,[1] in 1918, demonstrated in seven cases that painful appendectomy scars can be relieved by excision and suggested that inclusion of nerve fibers in the scar may be a cause of pain. Corner[2] emphasized the importance of persisting infection as a cause of painful scars, especially in amputation stumps, and was able to culture microorganisms about the regeneration neuroma in a wound which had been healed for three years. Corbett[3] pointed out that small nerves may be the site of painful neuromas that may be seen grossly. Clinton[4] found in cases of subcostal neuritis a small neuroma-like swelling of the intercostal nerves as they passed the tips of the last few ribs. Bancroft[5] reported four cases of painful right rectus incisions in which block anesthesia as a diagnostic procedure caused temporary cessation of pain. Relief followed excision of the scar. Neuromas were suspected although they were not seen in routine pathologic sections. Leriche[6] and, more recently, Pozzan[7] have reported favorable results in painful scars after the repeated injection of procaine hydrochloride. Thomas[8] relieved the pain of an inguinal scar by proximal section of the ilioinguinal nerve. Molotkoff[9] ventured the opinion that, in painful amputation stumps, abnormalities in the terminal ramification of the pain fibers were of more importance than neuromas of large nerve trunks. He advised high section of all the sensory nerve supply to the affected region and performed this procedure in eleven cases.

A few histologic studies have been reported by anatomists on nerve regeneration in cutaneous scars. Jäger and Traum[10] found that superficial regenerating fibers did not acquire encapsulated corpuscles but terminated in free endings. Tsunoda, Hamada, and Arimoto[11] noted that nerve fibers growing into scarred and inflamed areas acquire their protecting sheaths only at a late stage, if at all, as Corner[2] had previously mentioned. Klein[12] reported that minute amputation neuromas

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in the skin of experimental animals can be found easily if serial sections are impregnated by the special methods for nerve fibers. Quite recently Josefson[13] was able to demonstrate minute neuromas in the finger after amputation in three cases and after incised wounds in two cases.

TABLE I

CASES OF PAINFUL SCAR

CASE*	LOCATION	CAUSE	AGE OF SCAR (MO.)	DURATION OF PAIN (MO.)	TYPE OF PAIN	MICROSCOPIC FINDINGS	FOLLOW-UP (MO.)
1	Foot	Laceration	30	12	Sharp, spot	Small neuroma	36
2	Breast	Mastectomy	24	?	Two spots	Large neuroma	7
3	Breast	Mastectomy	17	9	Sharp, spot	Loose neuroma	0
4	Breast	Mastectomy	36	?	Sharp, two spots	Small neuromas	8
5	Anus	Incision	7	7	Spot on touch	Neuroma; exposed fibers	1
6	Finger	Laceration	12	4	Sharp, spot	Large neuroma	11
7	Scalp	Laceration	96	?	Sharp, spot	Long neuroma	1
8	Nose	Ulcer	12	3	Intense itching	Small neuroma	4
9	Ear	Puncture	24	24	Sharp spot and mild diffuse	Neuroma and inflammation	1
10	Neck	Excision of keloid	3	3	Spot on keloid	Neuroma	1
11	Chest	Laceration keloid	168	12	Diffuse on keloid	Inflammation	5
12	Abdomen	Hysterectomy	2	2	Spot	Inflammation	4

*Case 3 was an autopsy specimen. Case 11 had recurrence of pain three months after excision of the keloid. All other cases were free of symptoms.

MATERIAL AND METHODS

The present report is a study of twelve cases* of painful scars in various locations. Clinical tests were made of sensation, especially for points of hypersensitiveness to pinprick and to pressure. After excision of the painful area, the points of tenderness were examined histologically in serial section impregnated for nerve fibers by the Gros method.† Routine hematoxylin and eosin sections were made for comparison.

Small blocks of excised scar, properly oriented by drawings, were fixed immediately after operation in neutral 10 per cent formalin. After a period of fixation of at least four weeks, and preferably eight weeks or more, with several changes of formalin in glass-stoppered bottles, rather thick serial frozen sections were cut and placed in individual dishes. Each section was then impregnated separately under microscopic control.

In most instances a follow-up study of the postoperative course was possible and demonstrated relief of symptoms after excision. A preliminary note on the clinical aspects of these cases has been published.[14] In Table I the clinical data are summarized.

*Case 1 was treated at the University of Chicago Clinics, and the excised tissue was studied at the University of Pittsburgh. In three other cases the specimens were presented by others, in two of which I had the opportunity of examining the patient before excision of the scar.

†My thanks are due to Professor Jan Boeke and to Dr. L. K. Akkeringa of the University of Utrecht, Holland, for teaching me the refinements of the silver impregnation methods.

SUMMARY OF MICROSCOPIC FINDINGS

In Case 1 the segment, 6 by 2 mm., excised from a scar on the foot showed a small plexiform neuroma composed largely of single nerve fibers poorly supplied with protecting sheaths midway in the scarred corium and in close relation to a venule.

In Case 2 there was excision of two painful areas on a mastectomy scar. Fig. 1 shows a large regeneration neuroma deep in the scar just superficial to the subcutaneous fat. The size of the involved nerve bundles suggests their origin from a relatively large nerve trunk. Branches of this neuroma extend for considerable distances into the scar and are turned back before reaching the surface. They tend to be directed parallel to the densely packed collagenic fibers.

In Case 3, was a painful spot on a mastectomy scar, containing an excessive plexiform neuroma, from which radiated numerous long and undulating fibers compressed in dense scar tissue.

Fig. 1.—Case 2. Neuroma with rather large nerve bundles in mastectomy scar overlying subcutaneous fat.

On a mastectomy scar in Case 4 were two spots which contained several small neuromas immediately beneath the corium.

In Case 5 there was a minute nodule 2 by 2 mm. at the anal orifice which was exquisitely tender to touch as well as pressure. Sections showed deep in the nodule a neuroma of large nerve bundles. Fibers from the neuroma can be traced to the surface, a small area of which is eroded (Fig. 2). As can be seen, these small fibers apparently be-

come quite destitute of sheath cells as they approach the ulcerated surface. Several encapsulated end organs of the Golgi-Mazzoni type are also supplied by fibers from the region of the neuroma. There is some diffuse inflammatory infiltration, but it is not in close relation to the neuroma or its branches.

A painful spot on a stellate scar of the finger tip in Case 6 showed a dense globular neuroma about 0.6 or 0.8 mm. in diameter, embedded in dense collagenic fibrous tissue (Fig. 3). This was the case of Dr. H. Bowen.

In Case 7 a linear scar in the occiput contained an exquisitely tender spot. The specimen from Dr. J. P. Evans of Cincinnati showed an elongated dense neuroma just superficial to the galea and originating from a fairly large branch of an occipital nerve. This neuroma with its ramifications covers an area 10 by 3 mm.

Fig. 2.—Case 5. Neuroma in scar at anus, with nerve fibers exposed on ulcerated surface.

A scar on nose after x-ray treatment of ulcer in Case 8 contained a loose plexiform neuroma in its deep portions. The specimen was sent by Dr. J. A. Sasser of Conway, S. C.

In Case 9 there was a keloid of the ear which showed slight general tenderness and a single painful spot. There were numerous small foci of round and plasma cells, some of which, particularly at the margins, were adjacent to or surrounded small nerve fibers. The sensitive spot contained a small loose neuroma embedded in fibrous scar.

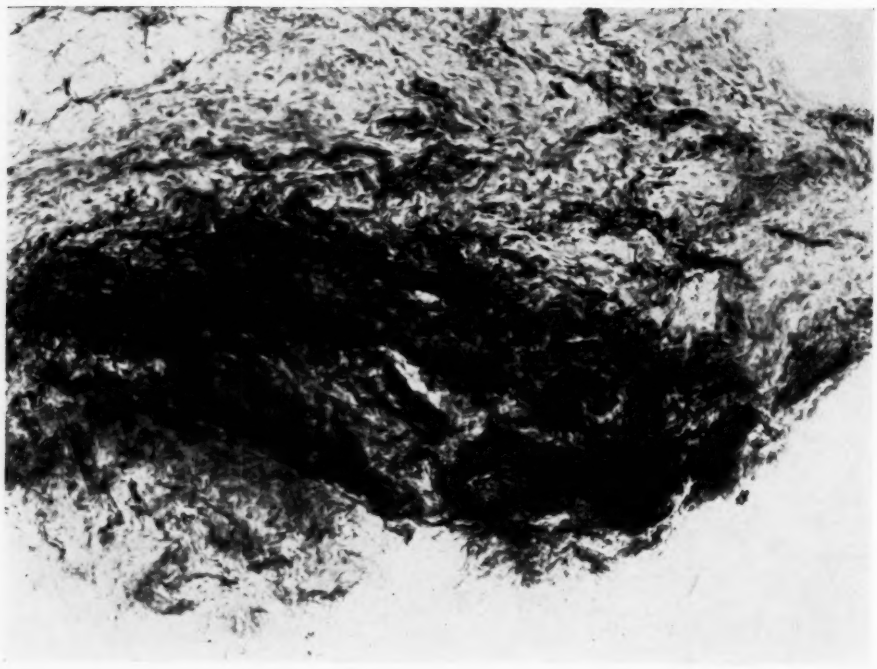

Fig. 3.—Case 6. Dense neuroma at base of scar on finger tip.

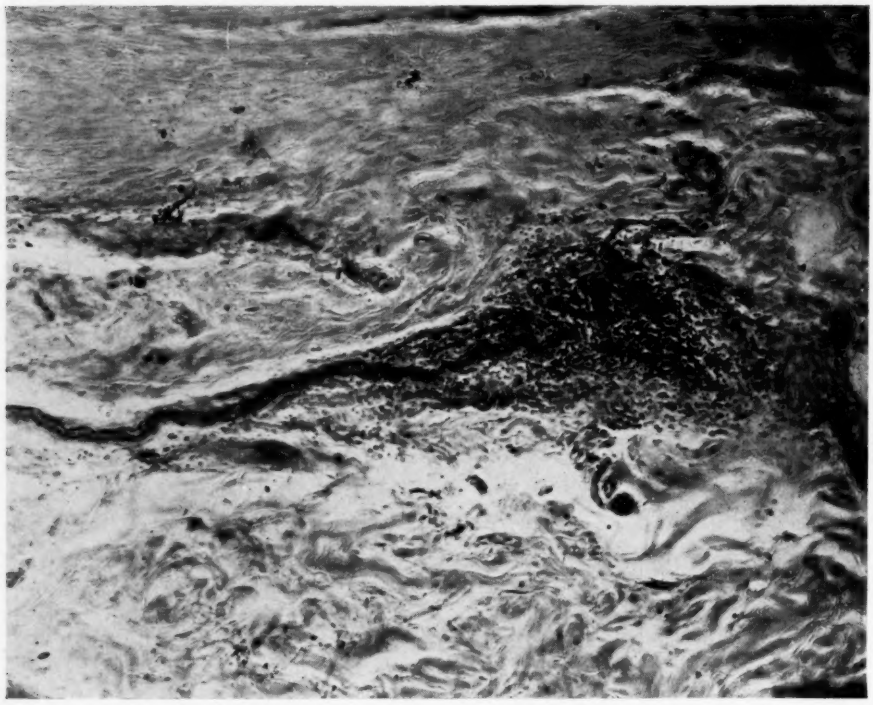

Fig. 4.—Case 11. Focus of chronic inflammation involving regenerating nerve fibers in keloid over sternum.

In Case 10 there was a massive keloid of the neck with a sensitive spot on the scar after partial excision. Excessive plexiform nerve regeneration with some inflammatory infiltration was present at the painful spot.

In Case 11 was a diffusely tender keloid over the sternum, with recurrence of discomfort three months after excision. Sections showed numerous regenerated nerve fibers coursing for great distances through the scar parallel to the surface. These fibers had fairly adequate sheaths and were single or in small bundles of from two to four fibers. Numerous areas of cellular infiltration, in some instances minute abscesses, surrounded the nerve fibers (Fig. 4). Neuromas were not seen.

In Case 12 there was a painful spot on a recently healed laparotomy scar, with many areas of inflammation about neurovascular bundles and regenerating nerve fibers. No neuromas were present.

DISCUSSION

The histologic findings in these cases indicate that pathologic forms of nerve regeneration in relation to cicatricial tissue are of importance in the production of painful scars. In ten of the twelve cases, a neuroma demonstrated microscopically at the point of maximum hyperalgesia seemed the chief cause of pain and tenderness. In two cases, inflammatory changes seemed responsible for the pain. One of these was a diffusely tender keloid, and the other, a recently healed laparotomy wound. It seems reasonable to assume, therefore, that a localized point of tenderness in an old scar in all probability indicates a neuroma.

The neuromas have been situated, for the most part, rather deep to the surface near the region where ingrowing cutaneous nerve fibers first encounter dense or infected scar tissue. Excision of a painful spot should, therefore, include the full thickness of the scar. Only that small portion of a painful scar containing a tender area need be removed to effect a cure. This fact becomes of importance when excision of the entire scar is undesirable and a lesser procedure on an ambulatory patient will suffice. Cases in point are long mastectomy or laparotomy scars, as well as multilinear stellate scars, where complete removal might entail complicated plastic maneuvers or unnecessary sacrifice of tissue. In recent cases of a few months' duration where the degree of pain does not make relief imperative, a period of observation may be indicated. Kredel and Evans[15] have reported in pedicle skin flaps that hyperalgesic points appearing at the borders of a scar may gradually disappear in the course of several months. The disappearance of pain in recent scars may be explained by the subsidence of inflammation or by the fact that the irritable regenerating nerve fibers atrophy or acquire their protecting sheaths of myelin and Schwann cells.

As regards the recognition pathologically of cutaneous neuromas, routine methods of examination are of little aid. Grossly, although reaching the size of several millimeters, the neuromas are difficult to distinguish from the scar in which they are embedded. Sections, unless cut exactly at the sensitive spot, may miss the neuroma altogether. Even

when through the proper area, thin sections stained by ordinary methods show little. Thicker sections may supply a clue if the sheaths of larger nerve bundles can be seen. But a neuroma whose fibers are deficient in sheath of Schwann cells can be demonstrated satisfactorily only by special methods for nerve fibers.

CONCLUSIONS

1. Painful and tender scars should be examined for local points of hypersensitiveness.

2. Simple excision of these sensitive spots will relieve the symptoms without removal of the entire scar.

3. Neuroma formation of tiny cutaneous nerves is the most important factor in the production of painful cutaneous scars of long duration.

4. Inflammatory changes may be the cause of pain in recently healed scars.

5. Prolonged healing with subsequent excessive scar tissue about regenerating nerves is apparently conducive to the production of painful neuromas.

6. Demonstration of minute cutaneous neuromas may require the use of special histologic methods for the impregnation of nerve fibers.

SUMMARY

The clinical and histologic findings are presented in twelve cases of painful cutaneous scars. In ten cases, microscopic neuromas were found at the points of tenderness. Relief of symptoms followed excision of the painful areas alone.

REFERENCES

1. Quain, E. P., and Eggers, C.: Painful Abdominal Scars, Mil. Surgeon **43**: 195, 1918.
2. Corner, E. M.: Infective Scar Tissue and Its Relation to Pains, Lancet **1**: 840, 1919.
3. Corbett, J. F.: Painful Scars, Minnesota Med. **4**: 682, 1921.
4. Clinton, M.: Subcostal Neuritis as a Cause of Abdominal Pain, J. A. M. A. **83**: 90, 1924.
5. Bancroft, F. W.: Painful Post-Operative Abdominal Scars, Arch. Surg. **20**: 289, 1930.
6. Leriche, R.: Physiopathologie des Cicatrices, Presse Méd. **42**: 1577, 1934.
7. Pozzan, A.: Sul Trattamento novocainico delle cicatrice dolorose, Arch. ital. di chir. **46**: 1, 1937.
8. Thomas, A.: Algie cicatricielle post-traumatique et post-operatoire d'abdomino-genital, Presse méd. **40**: 1869, 1932.
9. Molotkoff, A. G.: The Source of Pain in Amputation Stumps in Relation to Rational Treatment, J. Bone & Joint Surg. **17**: 419, 1935.
10. Jäger, H., and Traum, E.: Beitrage zur Nervenregeneration in menschlichen Hautnarben, Deutsche Ztschr. f. Chir. **196**: 364, 1926.
11. Tsunoda, T., Hamada, I., and Arimoto, R.: Experimentelle Studien uber die Veranderungen der Nervenendigungen in Narbengewebe, Virchows Arch. f. path. Anat. **268**: 751, 1928.
12. Klein, Marc: Sur la cicatrisation des nerfs cutanés, Bull. Soc. franç. de dermat. et syph. No. 7, 1, 1935.
13. Josefson, H.: Uber das Amputationsneurom der Fingernerven, Acta chir. Scandinav. **81**: 460, 1939.
14. Kredel, F. E.: Painful Scars, J. South Carolina M. A. **35**: 299, 1939.
15. Kredel, F. E., and Evans, J. P.: Recovery of Sensation in Denervated Pedicle and Free Skin Transplants, Arch. Neurol. & Psychiat. **29**: 1203, 1933.

EXPERIMENTAL STUDIES IN TRANSPLANTATION OF THE ADRENAL GLAND

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MANY attempts to transplant the adrenal gland in the dog have proved unsuccessful.[1-3] Failures have been attributed, in part, to the irritating properties of the degenerating medulla which produces massive necrosis in the tissues to which the transplant is made.[4] This has led some investigators to remove the medulla prior to transplanting the cortex of the gland, and it is now rather generally accepted that in small animals adrenal transplants undergo a necrosis which is followed by a regeneration from the capsule of the cortex only.[5-7] In the dog Levy and Blalock[8] succeeded in transplanting the kidney together with the adrenal to the neck, re-establishing the blood supply by suture of vessels. Subsequently the kidney was removed and viable transplants of both cortex and medulla of the adrenal remained. In a previous communication[9] successful transplantation in the dog of the adrenal to the ovary was described. This was accomplished by grafting without suture of blood vessels, and in such preparations viable transplants of both cortex and medulla were obtained. What appears at present to be the most satisfactory method of accomplishing such a transplantation is herein described and evidence of the functional activity of both the cortical and medullary portions of the graft is presented.

The experimental procedure is as follows: Healthy mongrel bitches are used. In the early experiments it was thought that small animals (5 to 10 kg.) were more suitable, but with more experience with the technique successful transplantations can be obtained in larger ones (15 to 20 kg.). Operations are performed aseptically under sodium pentobarbital (nembutal, Abbott) anesthesia. The procedure is divided into three operative stages. At the first stage the left adrenal gland is exposed through an oblique subcostal incision (Fig. 1 insert). The lower pole of the gland is freed by blunt and sharp dissection without dividing the lumboadrenal vein. The ovary and salpinx on that side are then mobilized and drawn up over the anterior surface of the renal pedicle to the bed of the adrenal (Fig. 2). In some of the early experiments a small fragment of each gland was then excised and the raw surfaces united with sutures (Fig. 2 *a*). It is more satisfactory to incise the free edges of the glands, partially bisecting them and then interlocking or "sandwiching" the two together (Fig. 2 *b*). This position is then maintained by mattress sutures of fine silk. The wound is closed and at a second operation, which is performed three or more weeks later, the

Presented at the meeting of the Society of University Surgeons at New York, N. Y., February 9 and 10, 1940.

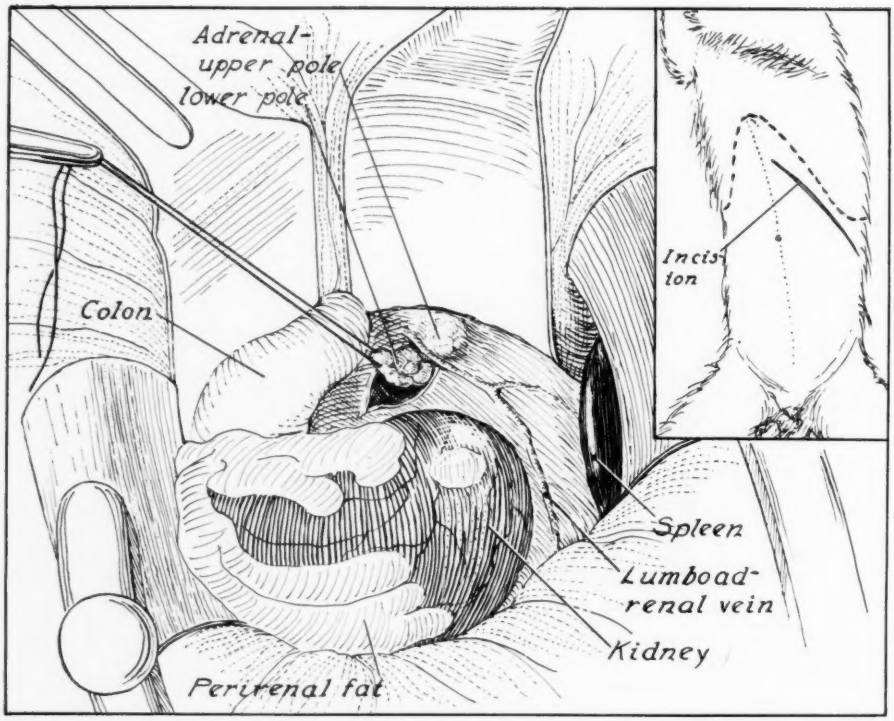


Fig. 1.—The lower pole of the left adrenal gland is exposed. Note that the lumbo-adrenal vein is not disturbed.

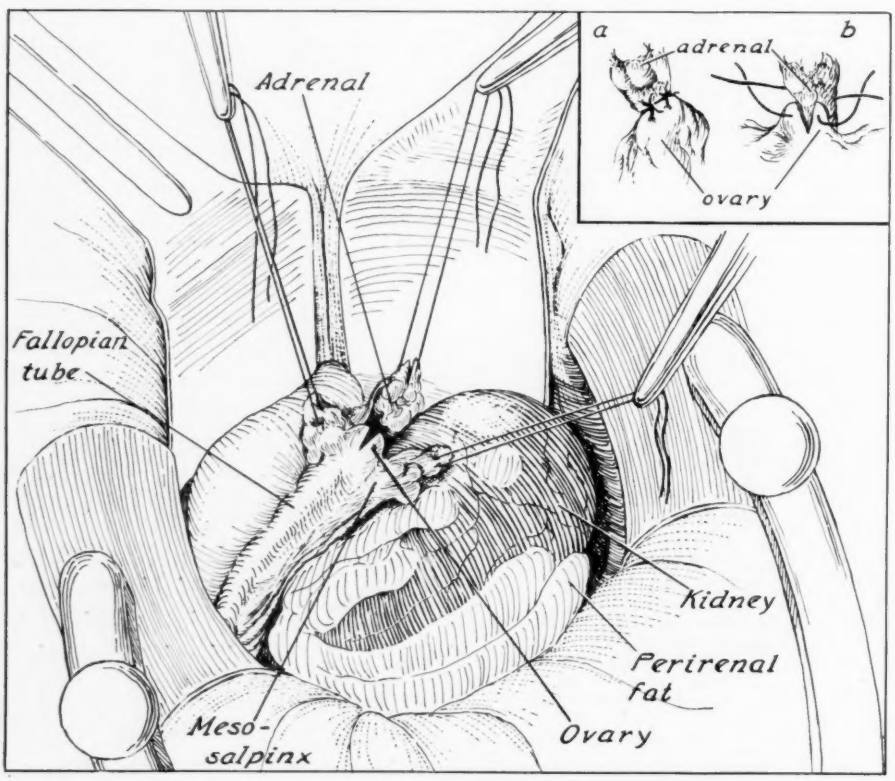


Fig. 2.—The ovarian pedicle is mobilized and the ovary and adrenal are about to be united by interlocking the partially bisected free edges of the glands.

adrenal is separated from its normal neurovascular supply and transplanted together with the ovary (Fig. 3) to the lower abdomen where it is sutured to the peritoneum of the anterior abdominal wall. The final stage, removal of the right adrenal, is performed about one month later. The right adrenal can be transplanted by the same technique, but more difficulty is encountered in freeing the right gland because of its proximity to the vena cava. For this reason usually the left adrenal is transplanted and the right adrenal excised.

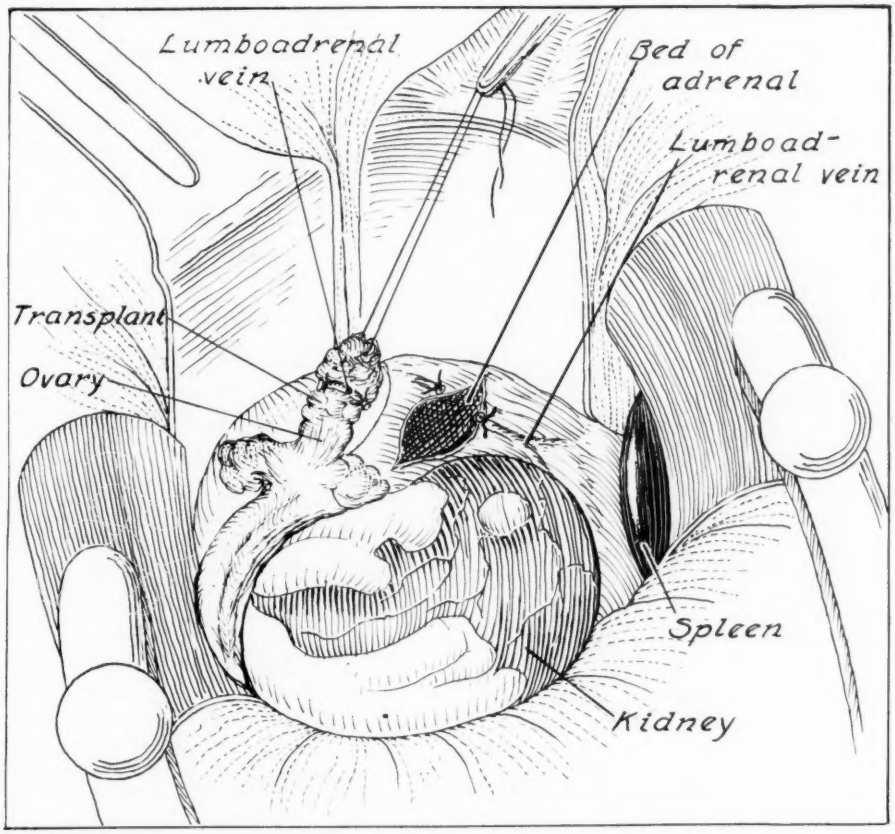


Fig. 3.—This, the second stage of the operation, is performed one month later, at which time the lumboadrenal vein is divided and the adrenal is separated from its normal neurovascular connection. The gland is then transplanted together with the ovary into the peritoneal cavity.

It is interesting that by this method there is no acute physiologic deficiency of adrenal tissue at the time the transplant is made, as the opposite adrenal is intact. Similar exceptions to Halsted's[10] "law of deficiency" have been noted by Levy and Blalock[8] and by Shambaugh.[11]

To date eight successful transplantations have been made. The animals appear to live indefinitely after transplantation of the left and excision of the right adrenal. One is alive and in good condition after twenty-three months. In four experiments the transplant was excised under aseptic conditions and the animals were allowed to recover from the anesthesia. Death from adrenal insufficiency occurred in two, five,

seven, and nine days respectively. Following excision of the transplant anorexia was the first symptom to appear. Gradually the animals became weak and apathetic, refusing all food and water. There was a terminal fall in the serum chloride and blood pressure in the two animals in which these determinations were made. The findings at autopsy were

Fig. 4.—Photomicrograph showing the contour of a transplant six months after transplantation. Fallopian tube, ovary, and adrenal are included in the section (×13, hematoxylin-eosin stain).

those usually associated with adrenal insufficiency. There was marked congestion in the viscera, particularly in the lungs, pancreas, and upper gastrointestinal tract, and to a lesser extent in the kidneys and liver. In no instance was accessory adrenal tissue found, although microscopic studies were made of tissue from the usual location of the glands.

The characteristic appearance of the adrenal gland is well preserved in the transplanted tissue. The medullary portion of the graft is always

smaller than normal, but the sharp demarcation between cortex and medulla is recognizable. On microscopic examination (hematoxylin and eosin and eosin-methylene blue) no significant variations from the normal are found in the cortical or medullary cells. The contour of a transplant removed six months after transplantation is shown in Fig. 4. In-

Fig. 5.—Photomicrograph showing the area between the adrenal and the ovary in a six-month transplant. Except for the presence of the silk suture, the two glands appear almost as a single organ. (×25, hematoxylin-eosin stain.)

cluded in the section are portions of the Fallopian tube, ovary, and adrenal. Note that the normal contour of the adrenal, including the medulla, is well preserved. Between the two glands is a thin layer of vascular connective tissue. How little the appearance of the two glands is altered by the transplantation is shown in Fig. 5, in which, except for the silk suture, ovary an adrenal appear as one organ. At a higher

power (Fig. 6) the cortical zones and medulla are more readily discernible. There is no hypertrophy or hyperplasia of the gland. The zona glomerulosa (Fig. 7) is well preserved without evidence of degenerative changes. There is less vacuolization of the cells in the fasciculata than usual, but here again no definite histologic evidence of malfunction is noted by the ordinary staining methods.

Fig. 6.—Photomicrograph showing the various layers of the cortex and the medulla in year-old transplant (×76, hematoxylin-eosin stain).

The excellent preservation of the medullary cells in these transplants (Figs. 6 and 8) indicates that, as Turner and his co-workers[12] have suggested, the principal reason for the failure of medullary transplants has been the difficulty in establishing, sufficiently soon, an adequate blood

supply to the central portion of the gland. By the method described above, a new blood supply has been partially established before the gland is deprived of its normal supply. The reason for the reduction in size of the medulla may be a certain deficiency of vascular supply, but this does not appear to alter the histologic appearance of the surviving cells (Fig. 8).

Fig. 7.—Photomicrograph showing the glomerular layer of the cortex in year-old transplant (×300, hematoxylin-eosin stain).

Ganglion cells are easily demonstrated in the capsule of the gland and unmyelinated nerve fibers are found in both the capsule and medulla. No myelinated nerve fibers are found. This is similar to the observation of Elliott[13] and Hollinshead,[14] who found that, although myelinated nerve fibers degenerate after division of the sympathetic nerve supply to the adrenal, there is a persistence of unmyelinated fibers. Such nerves probably arise from intrinsic ganglion cells. Levy and Blalock[8] also found only unmyelinated nerve fibers in transplanted adrenals.

The behavior of the animals following autotransplantation of the adrenal gland is not altered. Their general appearance is the same. They are as active as normal, eat well, and either gain or maintain their weights. None of these animals have contracted distemper, although several have been exposed to the disease at varying periods during their course in the laboratory. In two experiments the blood pressure was determined by the arterial puncture method before and at varying intervals for a year after transplantation. No significant variations were noted. The normal fasting levels of sugar, nonprotein nitrogen, albumin, globulin, calcium, and phosphorus in the blood have not been altered by transplantation of the adrenal gland in the two experiments in which these determinations were made.

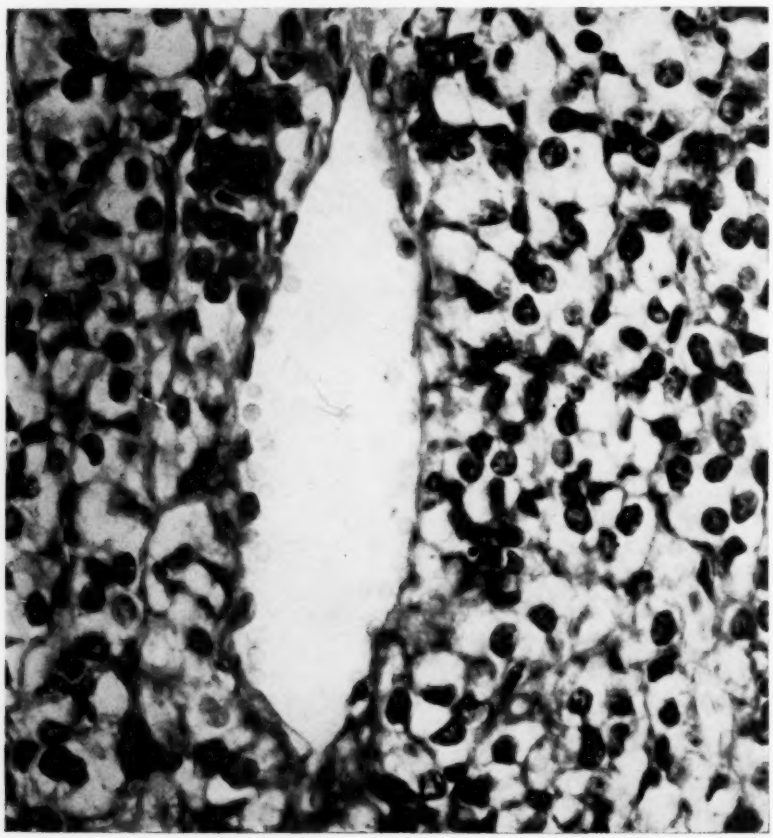


Fig. 8.—Photomicrograph showing the medulla of year-old transplant (×300, hematoxylin-eosin stain).

Although the general appearance and behavior of the animals is not altered and they seem able to withstand the ordinary hazards of laboratory existence, certain variations from the normal have been noted. These animals are extremely sensitive to sodium pentobarbital so that one-half the usual dose is sufficient to produce a full surgical anesthesia. Also, on a number of occasions the blood withdrawn from the jugular

vein has been so bright red as to be indistinguishable from arterial blood, and on determining the oxygen content of the arterial and venous blood one often finds an unusually low arteriovenous difference. This, however, is not a constant finding, for, after exercise or while under anesthesia, there may be a high arteriovenous difference. The total blood and plasma volume has been determined in two animals before and after transplantation of the adrenal. In both there was a slight decrease in volume.*

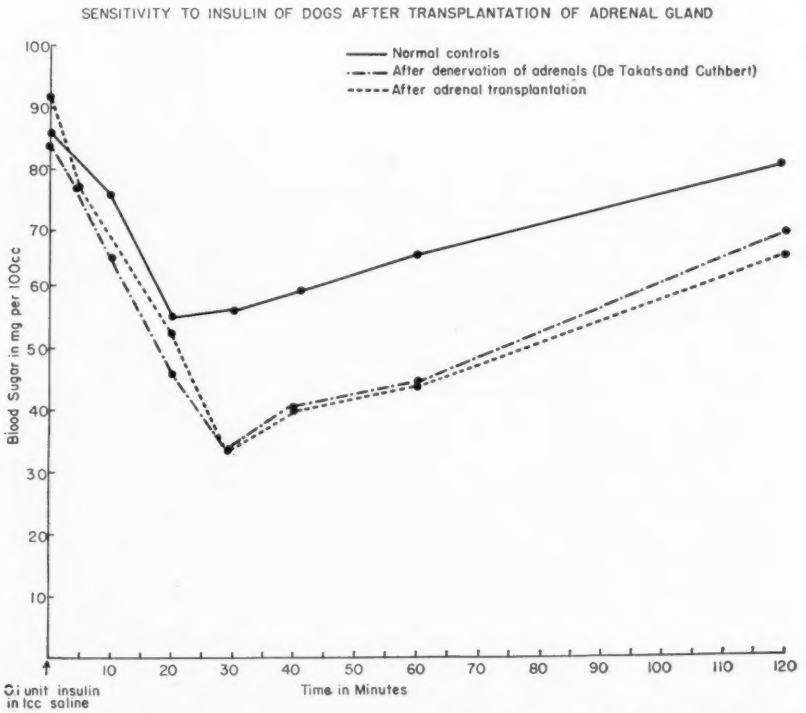


Fig. 9.—Curves showing the sensitivity to insulin of dogs as indicated by the fall in the blood sugar following the intravenous injection of 0.1 unit of insulin in 1 c.c. of normal saline solution.

As previously stated, the functional activity of the cortical portion of the transplants has been demonstrated in four experiments by the death of the animals following excision of the graft. No accessory adrenal tissue was found at autopsy and, if present, it obviously was not sufficient to maintain the life of the animal after removal of the transplant. Although the cells of the medulla appear viable, the function of this portion of the gland is considerably altered. It is well known that the secretion of adrenalin in response to various stimuli produces a transient hyperglycemia. Using this test as an indication of adrenalin secretion, Levy and Blalock could find no evidence of function of the medullary portion of transplanted adrenal glands. Even after the intravenous injection of acetylcholine, which is thought by Feldberg and

*The determinations were made by John G. Gibson, 2nd, by the method described by Gibson and Evans.[15]

his associates[16] to be the humoral transmitter of sympathetic impulses to the adrenal medulla, no hyperglycemic response was observed. Similar observations were made in the present study. The sugar tolerance of a dog following transplantation of the adrenal is similar to that seen after denervation of the adrenals.[17] Thus, there is a markedly increased sensitivity to insulin. The blood sugar curves following the injection of 0.1 unit of insulin intravenously in normal dogs, in those with transplanted adrenals, and in those with denervated adrenals is shown in Fig. 9. Note how closely the curves of the denervated and transplanted glands approximate each other. Although these various observations indicate that adrenalin is not secreted into the blood stream, they do not prove that the medullary cells are incapable of producing adrenalin.

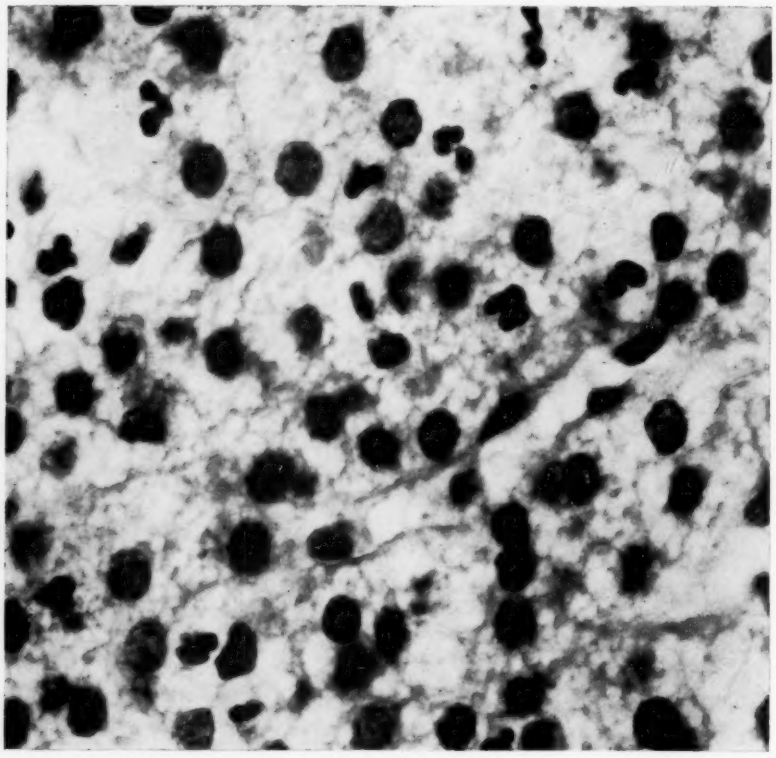
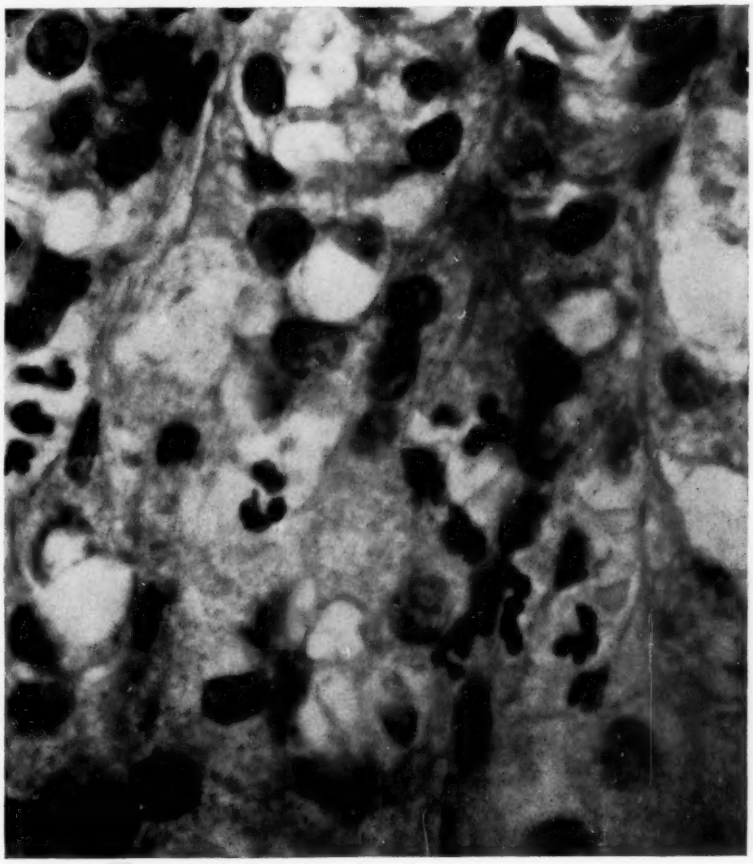


Fig. 10.—Photomicrograph showing the cells of the zona fasciculata of an intact adrenal gland ten hours after thermal trauma. There is swelling of the cortical cells and invasion of the area by polymorphonuclear leucocytes. (×1130, hemotoxylin-eosin stain.)

Despite the fact that the intravenous injection of acetylcholine in these experiments, as well as in Levy and Blalock's, failed to produce a hyperglycemic response, it seemed possible that adrenalin might be present in the gland and that the formation of acetylcholine at nerve endings within the medulla was necessary for active secretion into the blood stream. Accordingly, in two experiments the grafts were excised twelve and fourteen months after transplantation and assayed for adrenalin and acetylcholine. The assays were made by K. Lissak of the

Department of Physiology by a method which he has described.[18] By this method the normal adrenal of the dog gives a positive test for both adrenalin and acetylcholine-like substances. In the transplanted adrenal definite evidence of an adrenalin-like substance, in amounts of 80 γ (gamma) per gram, was found, but there was no evidence of acetylcholine. These observations a year or longer after transplantation indicate that the medullary cells not only appear viable histologically but are apparently capable of producing an adrenalin-like substance. The



A.

Fig. 11 *A* and *B*.—Photomicrographs showing the cells of the zona fasciculata in a six-month-old transplanted adrenal eight hours after thermal trauma. The same histologic changes noted in the intact adrenal are found in the transplanted adrenal. (×1130, hematoxylin-eosin stain.)

absence of acetylcholine together with the inability of the animal to mobilize adrenalin into the blood stream, although it is present in the gland, lends confirmation to the hypothesis maintained by Feldberg that acetylcholine is the humoral transmitter of sympathetic impulses to the adrenal medulla and that its formation at nerve endings within the medulla is essential for the release of adrenalin into the blood stream.

Although the exact role of the adrenal in various forms of shock is not clearly understood, it is known that following severe thermal trauma

pathologic changes in the gland are a constant finding at post mortem.[19, 20] Further evidence of the function of the transplanted adrenal is the fact that it shows the same histologic changes after thermal trauma as the normal gland. These consist of swelling of the cortical cells, particularly in the zona fasciculata and to a lesser extent in the zona reticularis, and an invasion of the area by polymorphonuclear leucocytes. The glomerular zone is not involved. These changes, as seen in a normal intact adrenal several hours after severe thermal trauma, are shown in Fig. 10. It is interesting that the transplanted adrenal, separated from its normal neurovascular connections and thus free from a bombardment by sympathetic stimuli, should show a similar alteration

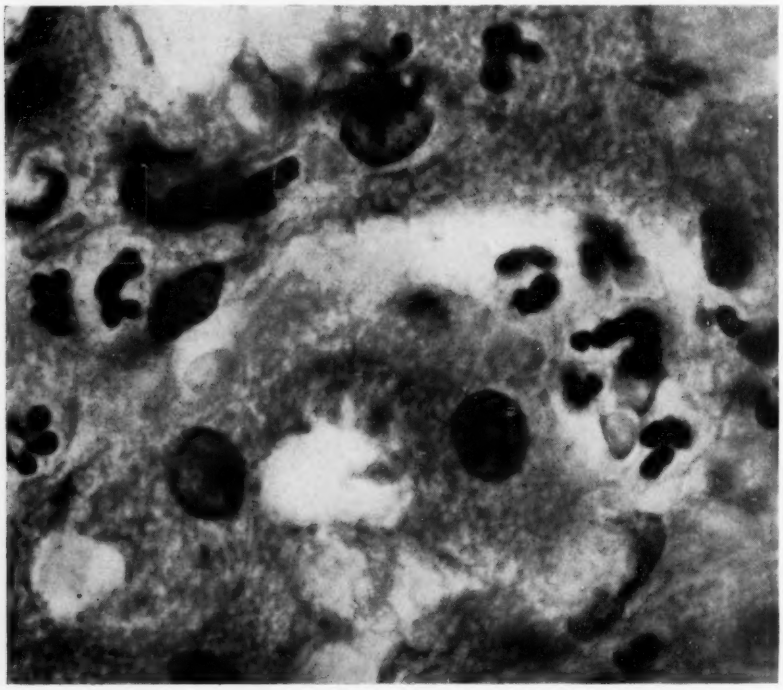


Fig. 11*B*.—See page 115 for legend.

of the cortical cells and infiltration with polymorphonuclear leucocytes (Fig. 11 *A* and *B*). This transplant was removed eight hours after the onset of shock from severe thermal trauma. The transplantation had been completed sixteen months previously and the animal had remained in excellent health until the time of the acute experiment. It is evident that the pathologic changes which occur in the adrenal after thermal trauma are not of neurogenic origin.

SUMMARY

The technique of autotransplantation of the adrenal gland of the dog by grafting it to the ovary is described in detail. Such transplants are composed of viable cells of both cortex and medulla and are sufficient

to maintain the life of the animal for indefinite periods of time. Successful autotransplantation of the adrenal by this method can be accomplished without a marked physiologic need for the graft at the time of transplantation.

The functional activity of the cortical portion of the grafts has been proved in four experiments after a period of four to fourteen months by the death of the animal from adrenal insufficiency following removal of the grafts. Although there is no evidence that adrenalin is secreted into the blood stream after transplantation of the adrenal, biologic assays of the grafts have demonstrated the presence of an adrenalin-like substance. There is no acetylcholine in the transplanted adrenal. Following the shock of severe thermal trauma, the same histologic changes are found in the transplanted adrenal as are noted in the normal intact adrenal.

The authors wish to thank Dr. Orville T. Bailey of the Department of Pathology for the photomicrographs and Dr. K. Lissak, formerly of the Department of Physiology, for the biologic assays of the transplants.

REFERENCES

1. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on Suprarenal Glands With Special Reference to the Functions of Their Interrenal Portions, Bull. Johns Hopkins Hosp. **25**: 287, 1914.
2. Oldberg, Eric: An Attempt to Transplant the Adrenal, Am. J. Physiol. **91**: 225, 1929.
3. Blodinger, I., Klebanoff, H. E., and Laurens, H.: Suprarenal Transplantation in the Dog, Am. J. Physiol. **76**: 151, 1926.
4. Grollman, Arthur: The Adrenals, Baltimore, 1936, Williams & Wilkins Company.
5. Jaffee, H. L.: Transplantation of the Guinea Pig Suprarenal and Functioning of Grafts, J. Exper. Med. **45**: 587, 1927.
6. Wyman, L. C., and tum Suden, C.: Studies on Suprarenal Insufficiency; Growth of Transplanted Cortical Tissue in Rat, Am. J. Physiol. **101**: 662, 1932.
7. Ingle, D. J., and Higgins, G. M.: Autotransplantation and Regeneration of Adrenal Gland, Endocrinology **22**: 458, 1938.
8. Levy, Sanford E., and Blalock, Alfred: A Method of Transplanting the Adrenal Gland of the Dog With Reestablishment of Its Blood Supply, Ann. Surg. **109**: 84, 1939.
9. Keeley, J., Dunphy, J. E., Quigley, T. B., and Bell, J.: Successful Autotransplantation of the Adrenal Gland in the Dog, Arch. Surg. **40**: 1, 1940.
10. Halsted, W. S.: Auto- and Isotransplantation, in Dogs, of the Parathyroid Glandules, J. Exper. Med. **11**: 175, 1909.
11. Shambaugh, Philip: Autotransplantation of Parathyroid Gland in the Dog; Evaluation of Halsted's Law of Deficiency, Arch. Surg. **32**: 709, 1936.
12. Turner, C. D., Haffen, R., and St. Amant, L.: Persistence of Medullary Tissue in Homotransplanted Adrenals, Proc. Soc. Exper. Biol. & Med. **41**: 474, 1939.
13. Elliott, T. R.: The Innervation of the Adrenal Glands, J. Physiol. **46**: 285, 1913.
14. Hollinshead, W. H.: The Innervation of the Adrenal Glands, J. Comp. Neurol. **64**: 449, 1936.
15. Gibson, J. G., 2nd, and Evans, W. A., Jr.: Clinical Studies of Blood Volume, J. Clin. Investigation **16**: 301, 1937.
16. Feldberg, W., Minz, B., and Tsudzimura, H.: Mechanism of Nervous Discharge of Adrenalin, J. Physiol. **81**: 286, 1934.
17. De Takats, G., and Cuthbert, F. P.: Effect of Suprarenal Denervation and Splanchnic Section on the Sugar Tolerance of Dogs, Arch. Surg. **30**: 151, 1935.
18. Lissak, K.: Effects of Extract of Adrenergic Fibers on Frog's Heart, Am. J. Physiol. **125**: 778, 1939.
19. Keeley, J., Gibson, J. G., 2nd, and Pijoan, M.: Effect of Thermal Trauma on Blood Volume, Serum Protein, and Certain Blood Electrolytes: Experimental Study of Effect of Burns, SURGERY **5**: 872, 1939.
20. Dunphy, J. E., and Gibson, J. G., 2nd: On the Pathogenesis of Shock. To be published.

Editorials

The Society of University Surgeons and the Need for a Surgical Forum

THE major portion of this issue of SURGERY is devoted to publication of papers of the second annual meeting of the Society of University Surgeons. This organization, the membership of which is composed of young men who have obtained their training in university surgical clinics, had its origin less than a year ago. The founders' group was comprised of surgeons from the following ten university medical schools: Chicago, Cincinnati, Columbia, Cornell, Harvard, Johns Hopkins, Rochester, Vanderbilt, Washington (St. Louis), and Yale. Fifty men were admitted to active membership at the first annual meeting held at Rochester, N. Y., in February, 1939. Upon arriving at the age of 45 years, men will retire automatically from active membership and become senior members. The qualifications for membership are defined as follows:[1]

1. The completion of at least one year as surgical resident in a university medical college hospital, maintaining a recognized resident system of postgraduate instruction.

2. Appointment to an official position on a surgical service of a university hospital.

3. Recommendation for membership by a member of the Society connected with the institution with which the applicant is associated.

4. A practice limited to surgery or the surgical specialties.

The aims of the Society of University Surgeons are the advancement of the art and science of surgery by:

1. The encouragement of its members to pursue original investigations both in the clinic and in the laboratory.

2. The development of methods of graduate teaching of surgery with particular reference to the resident system.

3. Free and informal interchange of ideas pertaining to the above subjects as a limited membership and common aims make possible.

One of the most urgent and obvious needs among surgical organizations in this country has been a surgical forum to which young men can bring their contributions and secure an audience. It is to be hoped that this newly formed Society of University Surgeons will satisfy, in part, this want. It is to be regretted that existing surgical societies have been slow to include a generous number of representative progressive young surgeons in their membership. For out of that group come the surgical leaders of tomorrow. The late William J. Mayo felt keenly

that the wisdom of age and experience should be exchanged freely with the enthusiasm of youth and that both old and young would benefit by the barter. The most original contributions to surgery, in the main, have their origins in the minds of young men. Exclusion of such men from membership in established surgical societies appears inconsistent with the expressed primary objective of all surgical societies; namely, the advancement of the art and science of surgery.

True enough, if a young surgeon has something worth while to say, surgical journals and other medical publications provide him with an avenue for making his ideas known. The particular merit of special societies is that their meetings furnish the individual the opportunity for crystallizing his ideas through discussion. It affords him also the opportunity of seeing and hearing and learning to know some of his colleagues. The interests of the membership, as a whole, of societies are served best by provision for the most original and stimulating papers within the scope of concern of its auditors, whether from the membership or by invitation, that the occasion can provide. It is to be admitted freely that the number of papers evincing real evidence of creative thought or distinctive achievement available for reading at the meetings of most societies is not numerous. Original thinking is the most difficult kind of labor and most of us spare ourselves its pains or are incapable of sustained thought in unchartered channels. In extenuation of this circumstance, it must be said that the yoke of duty and responsibility for the daily tasks hangs heavily on the surgeon. Much of his time is occupied in striving to perfect himself in those compartments of skill and knowledge which contribute to his effectiveness and the welfare of his patients.

The functions of a university are to teach and to think. Like a university, much of the activity of a society of like-minded individuals (including surgeons) is taken up by the interpretation or re-echoing of the recorded accomplishments of others. To this group of men, into which category most of us come, who essay to present papers before surgical gatherings, Glenn Frank has given the designation of "salesmen of knowledge." Moreover, the art and the science of surgery are in far greater need of the creative rather than of the interpretative mind. There appears to be a veritable plenitude of purveyors and caterers of surgical knowledge. In this connection the admonition of Cardinal Newman is not to be forgotten: "He who spends his day in dispensing his existing knowledge to all comers is unlikely to have either leisure or energy to acquire new."

It is interesting to contemplate the fortunes of Murphy and Halsted in their day. Resplendent, as one of the greatest surgical teachers of his time, Murphy's career reached its zenith within his lifetime and his star is growing dim already on the surgical horizon. The influence of Halsted is the lengthening shadow of a great man who made im-

portant contributions to his province of knowledge, but whose contemporary audience of appreciative admirers was not large. Halsted's star is rising and promises to remain luminous in the surgical firmament for a long time to come.

Much serious thought has been devoted recently by American leaders in surgery to the composition, objectives, and the potential influence of surgical societies. In a brilliant address entitled "Samuel Gross Looks in on the American Surgical Association," conducted in the manner of a Socratic dialogue, written in the Erewohnian vein of Samuel Butler, Graham[2] raised a number of questions concerning the nature of the organization and objectives of the American Surgical Association which are known to every group which has undertaken the responsibility of formulating a society which proposes to radiate a useful influence. In a very informative paper Phemister[3] has traced the origins and outlined the objectives and recounted the influences of the national surgical societies of a number of countries.

In his interesting monograph "The First Twenty-Five Years of the German Surgical Society" Trendelenburg relates how matters of composition as well as size of membership, audience, and nature of program were discussed by Langenbeck, Volkman, Bauer, Simon, and Billroth in the formation of the German Surgical Society. Professor Billroth inclined to the development of a free informal group in which chatty types of papers could be presented with a free admixture of intimate social intercourse. Langenbeck, on the contrary, insisted on a more formal type of organization which would radiate the influence of German surgery widely. The years have shown the wisdom of Langenbeck's judgment.

The purpose of the Society of University Surgeons, it is to be hoped, will concern itself more with the advancement of knowledge than with its diffusion. If this or any other constituted surgical group satisfies the pressing need for a surgical forum before which the most creative thought and original achievement in American surgery can secure an audience, it will fill a long-felt want, exert a large and important influence, and contribute richly to surgery.

Nowhere in the world have surgeons interested themselves so much in the experimental approach to surgery as here. Yet, no regular agency exists which makes it possible for young men interested in and pursuing the lifelong study of surgery to bring their researches before established surgical bodies. They can, it is true, often obtain an audience before a branch of the American Federated Societies comprising the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, and the American Society for Experimental Pathology. But, why should not these men have the opportunity of an audience from surgeons and why should surgeons be denied the privilege of hearing young men,

in their formative years, recite their own achievements? Must a young man receive recognition for his accomplishment before another audience before surgeons will deign to hear him? Surgical societies, whose primary purpose has been the dissemination of surgical knowledge, will do well to lend serious consideration to the matter of the establishment of a *surgical forum* before which the best that is new in surgery each year may be presented. Surgery has been advanced more by its science than its art. Why not admit young men whose training and original contributions to surgery indicate that they are made of sterling stuff freely to the privilege of surgical societies? We who are caterers and purveyors of surgical knowledge are too often guilty of "multiplying words without knowledge." Exclusiveness of membership in scientific gatherings and sterility of ideas are frequent companions.

The past never returns, but the character of the future can be determined, in part, by what is done in the present.

REFERENCES

1. Stabins, Samuel J.: Notes on "Articles of Incorporation, Society of University Surgeons."
2. Graham, Evarts A.: Samuel Gross Looks in on the American Surgical Association, Ann. Surg. **106:** 481-491, 1937.
3. Phemister, Dallas B.: The Development of National Surgical Societies With the Advent of Modern Surgery, Ann. Surg. **110:** 481-487, 1939.
4. Trendelenburg, Friedrich: Die ersten fünfundzanzigsten Jahre der deutschen Gesellschaft für Chirurgie. Berlin, 1923, Julius Springer.

—*Owen H. Wangensteen.*

Spinal Anesthesia: A Controversial Subject

SPINAL anesthesia has now been before the medical profession for a good many years. To be sure, for a number of these years it was in a poorly developed state as to drugs, indications, and technique of administration. This by gradual progress has now been largely overcome. While less so than in the past, there still exists almost a controversy, at least a striking difference of opinion, as to the value of spinal anesthesia, particularly in abdominal operations and especially in upper abdominal operations. There are those such as we in our clinic who employ spinal anesthesia in practically all abdominal operations, high and low. There are those who would not consider the employment of spinal anesthesia in abdominal operations; and there are all gradations between the two positions.

It is interesting that such a difference of opinion can continue to prevail and it has frequently interested me to try to analyze the situation in terms of why this difference exists. I have been led to do this because, as the head of a clinic, I have a moral responsibility for methods employed in it and because satisfaction with it, almost amounting to enthusiasm for it, forces me to try to ascertain why others do not have the approving interest in it that we in our clinic have.

I feel sure that the differences of opinion as to the value and safety of spinal anesthesia are largely related to the fact that proponents and opponents of the method frequently discuss the subject and evaluate the method without first establishing common criteria. Without the establishment of these common factors, opinions and decisions for or against spinal anesthesia are of little value and are bound to create attitudes which are not basically sound.

One cannot compare the results obtained with spinal anesthesia given by one who is expert in its use with spinal anesthesia given by the surgeon who is to operate and who then turns the patient over to a nurse or to an assistant to watch, or with spinal anesthesia given by one inadequately trained in its use. One cannot compare spinal anesthesia with any other anesthesia without being completely aware of the developments which have taken and are taking place in it—pontocaine, dilute nupercaine, and the as yet unproved but promising continuous spinal anesthesia (Dr. William T. Lemmon). It is wrong to assume that the introduction of drugs into the spinal canal as a method of producing anesthesia is in any way comparable with some of the other methods of anesthesia, for example with that produced by ether. One is a rough and ready, almost foolproof method of obtaining anesthesia; the other, a highly technical method capable of producing great harm unless given by a well-trained person.

Anyone discussing spinal anesthesia, we believe, must accept certain basic facts, one of the most important of which is that, when a spinal anesthesia is given, particularly for an upper abdominal operation, regardless of the expertness of the anesthetist, the anesthesia will occasionally extend to and beyond the desired level and produce paralysis of external respiration. If it has been administered by one experienced and expert in spinal anesthesia and its recent developments, this state will be promptly recognized. The anesthetist will carry the patient on by means of oxygen and the breathing bag until anesthesia ceases and voluntary respiration returns. As has been my own experience more than once, the operator will not know that this condition has existed until the operation is over. Should this occur, however, with a nurse or an inexperienced house officer observing the patient, failure to recognize the true state of affairs and to institute proper measures to meet it can and undoubtedly has resulted in fatalities. This is but a single example of many, evidencing the fact that spinal anesthesia must be given by those expert and experienced in its use.

We have now administered over 10,000 spinal anesthesias. Practically all abdominal operations, high and low, are done in our clinic under spinal anesthesia. There have been no fatalities attributable to spinal anesthesia. There are no patients in whom there exists a neurological complication related to the spinal anesthesia. I have personally performed many of the operations upon those patients to whom the spinal anesthesia has been given and am definitely convinced that, because of

the prolonged and complete relaxation of the abdominal wall and abdominal contents which can be obtained with it, it has reduced the mortality and morbidity of our abdominal operative procedures. I feel certain that many of the subtotal and total gastrectomies and resections of the lower end of the esophagus and cardiac end of the stomach would have been made much more difficult and dangerous had it been necessary to perform them under some other type of anesthesia.

I have no desire to agitate for the universal employment of spinal anesthesia in abdominal operations. I do greatly desire to agitate for the training and development of a greater number of anesthetists who are experts in spinal anesthesia of the various types. I am anxious to be certain when we are discussing spinal anesthesia critically that we who are for or against it are discussing it in the same terms. I would epitomize this into the statement that spinal anesthesia, certainly high spinal anesthesia, should never be given except by or under the direction of one experienced and expert in its use. When we are discussing this method of anesthesia and its complications or fatalities without this requirement of expertness and experience, we may unjustly discredit a method when the discredit should properly be assigned to an individual.

—*Frank H. Lahey, M.D.*
Boston, Mass.

To the Editors:

In a recent issue of Surgery (pages 282-309, February, 1940), there appeared a review on *Blood Transfusion* by Vary. My purpose in writing is to correct some statements it contains.

In the section on "faulty technique in pretransfusion testing" appear the sentences (page 296): "Isoagglutinins and isoagglutinogens may be absorbed or adsorbed by dissimilar or immunized cells or serum respectively for experimental purposes and the identification of subgroups and abnormal agglutinins. There are two subgroups identifiable as such by especially prepared sera; one of type A, called A_2; and one of type AB, called A_2B which are uncommon and so indistinct with the usual typing sera that one is apt to mistype them." The meaning of the former sentence is not clear to the writer. With regard to the subgroups, an understanding of which is required for routine blood grouping, a correct presentation would be as follows. There are two sorts of agglutinogen A, designated as A_1 and A_2, and these give rise to two subgroups in Group A; namely, A_1 and A_2, and two subgroups in Group AB, A_1B and A_2B. The agglutinogen A_2 is not uncommon, since in most white populations one-fifth of all Group A individuals belong to Subgroup A_2 and about one-fourth of all Group AB individuals to Subgroup A_2B. The reactions of blood containing agglutinogen A_2 in Group O and Group B sera (containing agglutinin anti-A) are weaker than those of blood containing agglutinogen A_1, but if high titered grouping sera are used for typing, as they should be, strong reactions are also obtained with bloods of Subgroups A_2 and A_2B.

As for the role of the subgroups in transfusion reactions, the review states: "Unquestionably, unrecognized subgroups account for a small number of serious incompatibility reactions." This is a point of some practical importance, and it may be remarked that, while from theoretical considerations such instances may very possibly occur, no case has yet been reported in which the subgroups of Group A were definitely shown to be responsible for hemolytic reactions. Incidentally the

article by Culbertson and Ratcliffe, cited as a reference for the statement regarding the relation of the subgroups to serious transfusion reactions, deals with quite a different subject.

In the same paragraph (page 296) appears: "The factors responsible for type determination when properly classified into three genotypes, A, B, and R, obey the Mendelian law of inheritance. There are two other factors called M and N which exist, independent of type, and are similarly inherited by assuming an added allelomorphic gene P." The actual facts are as follows: It is generally accepted that the heredity of the four blood groups, O, A, B, and AB, depends upon three allelomorphic genes, A, B, and R, which in combination give rise not to three but to six genotypes; namely, genotype RR, corresponding to Group O; genotypes AA and AR, corresponding to Group A; genotypes BB and BR, corresponding to Group B; and genotype AB, corresponding to Group AB. With regard to the agglutinogens M and N, these are inherited by means of a pair of allelomorphic genes, M and N. The agglutinogen P and its corresponding gene P have no connection with the heredity of M and N.

In the section on the early history of transfusion (page 282), Francesca Folli is credited with having performed the first transfusion in animals in 1654. Other writers have credited Francesca Folli with having performed the first transfusion from man to man; but in the article by Mayrhofer, who has made a careful study of this question (Mayrhofer, B.: Med. Welt. **12**: 473, 1938) it is asserted that Folli never actually carried out a transfusion either in man or in animals, but merely theorized as to the manner in which such transfusions could be done, just like other writers, such as Hieronymus Cardanus and Magnus Pegelius, before him (Scheel, P.: Die Transfusion des Blutes, Copenhagen, 1802). According to Zimmerman and Howell, the first authentic transfusion in animals was carried out not by Folli but by Lower in 1665, using dogs as the experimental animal (Zimmerman, L. M., and Howell, K. M.: History of Blood Transfusion, Ann. Med. Hist. **4**: 415, 1932).

Finally, with regard to the discovery of isoagglutination, full credit belongs to Karl Landsteiner, and it was primarily for this important discovery that he was awarded the Nobel Prize in Medicine in 1930, and the Cameron Prize by the University of Edinburgh. As has repeatedly been pointed out (Wiener, A. S.: J. A. M. A. **100**: 208, 1933; Blood Groups and Blood Transfusion, ed. 2, 1939; Ottenberg, R.: J. Mount Sinai Hosp. **4**: 264, 1937; Coca, A. F.: J. Immunol. **20**: 263, 1931) and as can clearly be seen by consulting the original article by Shattock (J. Path. & Bact. **6**: 303, 1900), Shattock's observations did not deal with isoagglutination but with rouleaux formation. In Landsteiner's papers (Zentralbl. f. Bakt. **27**: 357, 1900; Wien. klin. Wchnschr. **14**: 1132, 1901), the Groups O, A, B are described; the fourth and rarest group, AB, was discovered not by Jansky but by Decastello and Sturli (München. med. Wchnschr. **14**: 1132, 1902), the latter a pupil of Landsteiner's who continued the work at Landsteiner's suggestion. The main contribution of Jansky and Moss was that they suggested two different designations of the groups by numbers I, II, III, and IV. In order to avoid confusion these are now replaced by the International Nomenclature by letters O, A, B, and AB in scientific publications, this nomenclature being advocated for general use by the American Medical Association (Report of the Committee on Medicolegal Blood Grouping Tests, J. A. M. A. **108**: 2138, 1937).

The above remarks are not intended to detract from the value of a review that contains valuable information on a subject which is still in development and of considerable interest for the surgeon.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

SOME CURRENT PROBLEMS OF ANESTHESIA

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(Continued from the June issue)

ORGANIC EFFECTS

Blood Changes During Anesthesia.—

Blitstein (1937) has made a very long study of physicochemical alterations of the blood after surgical interventions under various anesthetics. It is difficult to evaluate such blood changes when the setup is complicated by surgery. This does not imply that such studies are valueless, but it does mean that it is virtually impossible to estimate their worth unless the reviewer is personally familiar with the controls used and the clinic where they were carried out. In any case, it is dangerous to draw inferences as to the role of the anesthetic from such studies.

Blood Concentration Influenced by Ether and Barbiturates: Many circumstances can effect rather wide variations in the concentration of the several elements in the blood. Bollman, Svirbely, and Mann (1938) point out that the rapidity of the variations in plasma volume caused by withdrawal of water from the tissues to the blood or the loss of fluid from the blood to the tissues is less generally appreciated. They have considered experimentally the influence of ether and amytal anesthesia upon blood concentration in dogs.

Light amytal anesthesia usually produced a definite reduction in the hematocrit value. Typically there was a definite increase in the plasma volume. These changes were of the same relative magnitude, so that the total circulatory blood volume appeared only slightly changed. Following splenectomy there occurred a smaller decrease in the hematocrit values and about the same increase in total plasma volume as occurred in the intact dog.

Light ether anesthesia of normal dogs resulted in an increase in the hematocrit value and a decrease in total plasma volume. There was little if any net change in blood volume. Splenectomized dogs receiving ether anesthesia showed similar changes in blood concentration with the exception that the hematocrit values did not show enough change to indicate an increased volume of cells in the general circulation. Normally a more marked decrease in the plasma volume and in the total circulating blood volume occurred than in the intact animal under similar circumstances.

In a study of the total numbers of erythrocytes and leucocytes per cubic millimeter before and after ether and sodium amytal anesthesia, Higgins and Corwin (1937) have utilized rats and rabbits before and after splenectomy. The blood counts (excepting erythrocytes in rabbits) in the intact animals have been found to be significantly lower under amytal than under ether anesthesia. Following removal of the spleen, they conclude that this organ is not an important site for sequestration of erythrocytes from the peripheral blood of rats and rabbits under sodium amytal anesthesia. They conclude further that under sodium amytal the spleen plays an important role in the sequestration of leucocytes in rats but not in rabbits. Increase in plasma volume dilutes the circulating blood elements under sodium amytal anesthesia, resulting in lower counts. The increase in plasma may also account for the distended spleen encountered under the barbiturate.

Hamlin and Gregersen (1939) report that the intravenous injection of nembutal to produce anesthesia causes a 10 per cent increase in plasma volume in normal cats, but an increase of only 2 per cent or less in sympathectomized animals.

McAllister (1938), in studying the effect of ether anesthesia upon the volume of plasma and extracellular fluid (Gregersen's spectrophotometric method), found in twenty-three experiments on dogs that one hour of anesthesia caused an average decrease in plasma volume of 11 per cent. Calculating the decrease in plasma volume from the rise in concentration of the serum proteins, the fluid loss averaged 9.3 per cent. He found further that the hematocrit rise was about twice that which could be accounted for by the decrease in plasma volume. Following splenectomy, this discrepancy became less.

Few observations have been made of the changes in body fluid of patients which result from anesthesia (cf. McAllister on animals), although the changes produced in concentration of many of the components of the blood have been considered at length. While studies of patients undergoing operation and anesthesia are open to certain obvious criticisms, the findings recorded by Stewart and Rourke (1938) are nevertheless of much interest. Studying sixteen patients who underwent ether anesthesia and surgical operation, they find that a notable reduction in blood volume occurs without appreciable change in the physical or chemical character of the blood (see below). The average reduction in volume was 13.4 per cent. Concentration of the structurally important components of blood plasma—protein, sodium, and chloride—were accurately maintained. This stability makes it evident that the reduction in blood volume is not due to dehydration. The blood loss occurring in the course of the operation was measured in thirteen of the cases and was not adequate to account for the volume decrease.

Interstitial fluid volume as measured in these patients by the thiocyanate method showed an increase of surprisingly great proportions. Either a reduction in the extracellular ions, sodium, and chloride, or an extracellular increase in concentration of the largely intracellular potassium ion, would be expected here. Stewart and Rourke found neither condition and conclude that this apparent increase must be open to question, although it is so large and so constant a finding that it is probably true.

In agreement with the observations of others they found that the concentrations of serum potassium and bicarbonate are significantly reduced.

A striking feature of this study is the extraordinary stability of the composition of the blood, despite the great demands imposed upon the homeostatic mechanisms in the course of anesthesia and operation.

Evipal and Reported Anemia: Dallemagne (1938) continues to state that evipal anesthesia may be followed by a grave degree of anemia.* Beecher (1938) was, however, unable to confirm this observation and found, on the contrary, that, even when a more intensive and more prolonged exposure to evipal was carried out than that employed by Dallemagne, detailed studies of the erythrocyte count, the cell volume, the mean corpuscular volume, the hemoglobin, and the oxygen capacity all failed to show any anemia-producing effects of evipal.

Blood Glutathione: Giuffrè (1939) reports that subcutaneous infiltration with solutions of novocain, pontocaine, and percaine causes a more or less notable diminution of the blood glutathione, less with those of lower toxicity, novocain and pontocaine, and more for percaine.

Carbohydrates: Macintosh and Pratt (1938) have reviewed the subject of carbohydrate metabolism during anesthesia. This is discussed further in the following section on the liver, and in particular in the work of Hrubetz and Blackberg recorded there.

I. A. Lerman (1936) has studied the influence of sodium barbital, chloroform, and ether upon glycemia in dogs. The barbital was administered by mouth. The rate of absorption is too uncertain by this method for use in such a study as this. Tables of data such as are presented in the article are also of little value unless the changes observed are established as significant by statistical methods.

Defandorf (1938) reports that the administration of anesthetic doses of paraldehyde to healthy, fasting dogs produced a small elevation of the blood sugar level. This was greatest during the first hour and averaged 16 mg. per cent. High elevations of blood sugar occurred in poorly nourished animals under paraldehyde anesthesia.

Glycosuria did not occur in normal dogs during paraldehyde anesthesia. Significant quantitative changes in the rate of urine secretion were not observed.

*Study made on dogs.

Blood Ascorbic Acid: It has been stated previously by Ecker, Pillemer, and Wertheimer that a close parallelism between complement activity and ascorbic acid content is to be found in guinea pig sera. In the present paper (1938) they provide data showing that a rise in ascorbic acid content of guinea pig serum occurs after thirty minutes of ether anesthesia; yet no marked changes in complement titers were observed. Zilva (1935) found that when l-ascorbic acid was injected into etherized guinea pigs the urinary excretion of the l-ascorbic acid was increased. Bowman and Muntwyler (1935) have found that the urinary excretion of ascorbic acid in the dog following ether anesthesia is increased ten- or fifteenfold.

Kasahara and Gammo (1938) report that the vitamin C content of cerebrospinal fluid is not essentially lowered by ether and chloroform anesthesia in monkeys and rabbits.

The Gastrointestinal Tract.—

Oettel (1935) has made the following observations on the influence of anesthesia and laparotomy on the motility of small intestines. In the normal small intestine of the dog it was shown that under general anesthesia (chloroform, ether, evipan, pernocton, chloralose, avertin, urethane, paraldehyde, chloretone) the intestines are also anesthetized (paralysis of tonus until a resting position in "diastole" is assured).

Acetylene does not paralyze the intestine of the fistulous dog; even in deep acetylene anesthesia, the intestine goes on working normally.

Morphine, in unanesthetized fistulous dogs, in contrast to the true anesthetics, never causes a paralysis of tonus, even in stupefying doses (about 5 mg. per kilogram), but always an increase in tonus until a spasm lasting for hours occurs (position at rest in "systole").

The movements of the intestine registered under anesthesia after opening the abdominal cavity and cutting the intestine are distinguishable qualitatively and quantitatively from the normal intestinal activity. As a paralysis of the intestine appears after laparotomy even under acetylene anesthesia, the injury to the intestinal motility is dependent upon the operative interference.

The small intestine, entirely paralyzed by anesthesia and operation, regains its ability of rhythmic movement by subcutaneous injection of morphine. In a laparotomy under morphine anesthesia, movements of the intestine can be registered accordingly, which correspond in their main type to the normal activity of the intestine, but are characterized by gradual increase of tonus (typical effect of morphine).

The movements of the intestine appearing after the death of the animal are entirely different from the normal intestinal motility.

Conclusions regarding intestinal motility and the action of substances on the intestine in situ can be drawn only with great reservation from acute experiments in an anesthetized, laparotomized animal.

Weisel, Youmans, and Cassels (1938) have studied in dogs the effects of morphine, scopolamine, and cyclopropane upon the motor functions of the intestine, considering separately tonus and nonpropulsive and propulsive movements, since these may be affected unequally and in opposite directions. Morphine (1 mg. per kilogram), they find, produces a rise in tonus and an increase in both propulsive and nonpropulsive intestinal movements. This increase is followed in from ten to twenty minutes by a period during which propulsive movements are nearly absent, although the tonus remains high and the nonpropulsive movements are still above normal amplitude. These findings are in agreement with those of other investigators.

Scopolamine (gr. $\frac{1}{50}$ to $\frac{1}{100}$ per dog) quickly produces complete inhibition of movements and lowered tonus.

Morphine and scopolamine together produce an effect about the same as morphine alone.

Cyclopropane anesthesia produces a decrease in intestinal tonus and inhibits all types of movements in unpremedicated dogs. In deep anesthesia the inhibition is complete. When premedication with morphine and scopolamine has been used, cyclopropane anesthesia does not lower the high tonus of the bowel, but it partially inhibits nonpropulsive movements. Propulsive movements are absent.

Termination of cyclopropane anesthesia is followed by an immediate return of the nonpropulsive movements to the preanesthetic level. Recovery of tonus is rapid, while recovery of propulsive movements may occur at once or may require several hours in premedicated or unpremedicated animals.

While Peoples and Phatak (1935) have shown that isolated rabbit's intestine in cyclopropane and oxygen increases in tonus, it seemed desirable to repeat this in the intact animal. Burstein (1938, a), using dogs with Thiry-Vella fistulas of the jejunum or ileum, observed that cyclopropane causes an increase of both intestinal contractions and tone in the first two planes of third-stage anesthesia. In the lower planes of this stage, contractions are inhibited, but tone is maintained. It is interesting to compare this with ether which causes an abolition of the contractions in all planes of the third stage. (See above reports.)

Sleeth and Van Liere (1938) have carried out in dogs a comparative study of the effects of various anesthetic agents upon the emptying time of the stomach. Using a standard barium meal and making observations with the fluoroscope, they found under all agents a prolongation of the emptying time: chloroform by 64 per cent, ether by 40 per cent, and ethylene, cyclopropane, and divinyl ether by about 7 per cent. They also report a 15 per cent increase for nitrous oxide. This is scarcely worth inclusion, for only 5 per cent oxygen was administered with the nitrous oxide. It represents the effect of nitrous

oxide anesthesia plus severe anoxia. This paper contains some indication of the probable reasons for the more frequent postoperative gastrointestinal disturbances following ether, for example, than following cyclopropane or ethylene.

A marked inhibition of the gut during anesthesia has already been described. Emerson (1936) has shown in a study on rats that ether anesthesia increases significantly the reduction processes taking place in the rats' intestines. These reduction processes, following one hour of "surgical" ether anesthesia, reach a peak with the fecal sample taken six hours after induction of anesthesia. Some augmentation over those of untreated controls is shown up to the eighteenth hour following anesthesia. It is doubtful if one can draw any analogies in man, for the definite and regular biochemical effects of the functional disturbance in rats have not been identified in man.

Burstein (1938, b) has studied the effect of divinyl oxide on intestinal activity in vivo. He recalls that Peoples and Phatak have observed that the tone of an isolated intestinal segment is increased by divinyl oxide; whereas, in the present study Burstein finds, contrary to the in vitro studies, that all animals (six dogs) showed effects identical to those obtained with ether (diethyl)—diminished muscular tone and complete inhibition of intestinal contractions during all planes of surgical anesthesia.

Ethyl alcohol diminishes the tone and peristalsis of the human stomach. Barlow (1936) found this true for all doses studied. Interestingly enough, he found that whisky containing equivalent amounts of alcohol actually increased gastric tone and motility, and it was only after relatively large doses of whisky that the depression characteristic of alcohol appeared.

Asteriadès (1938) recounts several cases of postoperative ileus successfully treated by spinal anesthesia.

In regard to gastrointestinal disturbances, Taylor, Bennett, and Waters (1937) find that "total nausea and emesis" under cyclopropane occur in 28.7 per cent of the cases, whereas under ether the figure is 40.6 per cent. They find the nausea to be less severe and of shorter duration under cyclopropane than under ether.

The Liver.—

In any determination of the effects of anesthesia upon hepatic function a number of considerations are inescapable. Is the liver damaged by the operative intervention, for example? The operative factor can be controlled with some degree of completeness by a large series of similar cases under various anesthetic agents. Considerable doubt can be raised fairly of whether measurement of one of the liver's numerous functions gives a useful picture of damage produced by the anesthetic agent. This is aside from reasonable questions of sensitivity of the tests used, duration of anesthesia, age and condition

of the patient, etc. Complicating these uncertainties is the possibility that damage present may have been produced by inadequate oxygen intake, by circulatory derangements, by shock, and so on. In such a confusing situation "negative" findings prove little, and "positive" findings must be interpreted guardedly. At the present time the tests probably used most often in suspected liver damage in the presence of jaundice are the icterus index, the van den Bergh test, and the galactose tolerance test, while in the nonjaundiced patients the bilirubin and bromsulphalein tests are often used. Some simplification of these problems is necessary before any attack can be made conveniently upon them. Coleman (1938), as others had before him (Bourne and Raginsky), decided that the bromsulphalein excretion test was worth employing. In using only 100 cases covering six anesthesia combinations, his data are open to the criticism of inadequacy; however, it is probably fair to draw some inferences from the forty-nine patients who received nitrous oxide-oxygen-ether, the twenty-seven who received nitrous oxide-oxygen, the thirteen who received avertin, and the eight who received spinal anesthesia. He finds in man that avertin produces hepatic damage in a higher percentage of cases and to a greater degree than nitrous oxide-oxygen-ether, than nitrous oxide and oxygen, and than spinal anesthesia, and that the liver is slower in recuperating from damage produced by avertin than from the others. Interestingly enough, he finds nitrous oxide-oxygen less damaging to the liver than spinal anesthesia. (Data on the blood pressures encountered would be of interest.) Whatever the anesthetic agent used, the longer the duration of use, the greater the chance of liver damage. The older the patient, the greater his chance of hepatic damage will be.

Reynolds, Schenken, and Veal (1938) report a high percentage of focal liver necrosis in mice anesthetized by pentothal; this was not so with evipal or amytal.

Forbes, Neale, and Scherer (1936) describe a liver concentrate which, on injection into rats, protects them to a great extent against carbon tetrachloride and chloroform poisoning. What the substance is or how it protects is not known. It is believed not to be choline, glucose, or the pernicious anemia factor.

The suggestion that low blood amylase is associated with liver damage has led Cajori and Vars (1938) to produce liver damage in dogs with chloroform anesthesia and to observe simultaneous changes in blood amylase. They found that the amount of decrease of serum amylase was related to: (1) duration of the anesthetic; (2) elapsed time following administration of the anesthetic; (3) whether the chloroform was volatilized with air or oxygen (greater decrease when air was used); (4) degree of liver damage as revealed histologically. From these facts and other evidence obtained it seems probable, although by no means certain, that the low serum amylase level found was the result of changes in the liver induced by chloroform.

Liver esterase was found to be decreased in livers made severely necrotic by chloroform.

Bourne, McDowell, and Whyte (1937) recount earlier work of Bourne and Raginsky in which the following conclusions in regard to vinyl ether were made (the liver function was tested with bromsulphalein dye):

1. Vinyl ether anesthesia in normal dogs does not appreciably alter liver function.

2. If cyanosis occurs during this anesthesia, liver necrosis may result.

3. Vinyl ether anesthesia neither enhances previous liver damage nor delays recovery from it.

4. Vinyl ether anesthesia does not have a greater effect upon the liver function of starved dogs than it does in normal dogs.

They describe Molitor's work (personal communication and apparently previously unpublished). Molitor placed a cannula in the bile duct, and, with a drop recorder to indicate changes in rate of flow, he proceeded to measure and weigh the bile formed. This was reinjected into the duodenum. A control animal showed a pronounced decrease in bile flow in the first hour and slow and gradual increase in the next two hours. Under chloroform an immediate decrease in bile flow occurs; this persists even after the anesthesia is withdrawn. Under ethyl ether there was a slight initial decrease and a subsequent increase in bile flow as in the control animal. Under vinyl ether there was no change in bile flow, even with two hours of profound anesthesia. With 95 per cent nitrous oxide and 5 per cent oxygen there was a prompt drop in bile flow, almost complete cessation. This was then changed to 80 per cent nitrous oxide and 5 per cent oxygen + vinyl ether to produce deep anesthesia, and the bile flow was resumed, reaching its normal rate in five minutes.

Oxygen and Hepatic Function During Anesthesia.—

An interesting historical review of the relationship of anesthetic agents to liver function is presented by Bourne (1936). His concluding remarks are of interest here: "It can be said that, with the exception of cyclopropane, all anesthetics may cause some impairment of liver function. But this should not be taken too seriously, except in the case of chloroform. . . ." The protective action of adequate oxygen is well established. Oxygen shortage may cause irreparable liver damage.

After a study of the effects of divinyl ether anesthesia in dogs, Bourne and Raginsky (1935) conclude that the agent does not alter liver function appreciably in dogs that are normal, unless the anesthesia is accompanied by anoxia, in which case liver damage occurs.*

*See Ravdin et al.

They found divinyl ether to be an unsatisfactory anesthetic agent for use with dogs. The animals were too often either about to awake or about to die. The safe anesthesia zone appeared to be narrow, narrower than for man, they conclude. When death occurred following the use of too great a concentration of the drug, it was apparently due to respiratory failure closely followed by cardiac failure.

Ravdin, Vars, Goldschmidt, and Klingensmith (1938), in continuing their studies of anesthesia and liver damage, have taken up the problems of whether the use of oxygen as the volatilizing agent in chloroform anesthesia has a sparing effect upon liver glycogen, or whether it modifies or prevents fatty infiltration of the liver and whether it influences the level to which the blood sugar might rise during anesthesia and the rapidity of the fall following anesthesia. Dogs and white rats were used in the studies.

They report that during chloroform anesthesia the blood sugar level is the same whether air or oxygen is used in volatilizing the agent, although, of course, when anoxia exists great increase occurs in the blood sugar level. Rise in blood sugar during anesthesia was not proportional to the original glycogen concentration.

Ravdin (1939), in summarizing earlier work by himself and his associates, says that adequate oxygen in the inspired air during anesthesia will have almost as much protecting action on the liver as a high carbohydrate intake.

Influence of Diet on the Action of Anesthetic Agents, With Some Remarks on Hepatic Function.—

There is nothing new in the demonstration that diet can influence the physiologic action of drugs. Many examples of this can be recalled. For instance, there is the work of Salant and Swanson (1918). In studying the toxicity of sodium tartrate, they used cats, rabbits, and rats and found that diets rich in sugar were efficacious in decreasing the toxicity of the tartrate. The toxicity of sodium tartrate was most marked on a diet of oats, hay, and cabbage. Resistance to the tartrates was much higher when the animals were fed a diet of carrot leaves. Then, there is the observation of Blatherwick and his associates (1924) who presented data to show that rabbits fed on a base-forming diet are less resistant to insulin than animals fed on an acid-forming diet. This observation was confirmed by Geiger and Kropf (Hjort et al. [1939]).

It is of some interest to consider the accounts of the influence of diet on the action of anesthetic agents. Benecke (Hjort) found that the toxicity of avertin was apparently uninfluenced by unbalanced diets. This is somewhat surprising when one considers the similarities of the toxic effects of avertin and chloroform, and surprising in the light of the work of Ravdin and his associates (to be described in some detail below) and others regarding the influence of diet on chloroform poisoning.

Continuing on the same theme, it is interesting to find that Cutler (1932), while not able to demonstrate any consistent differences in the amount of liver damage produced by carbon tetrachloride in dogs on various diets, was able to show that the severity of the symptoms and the number of the deaths secondary to the liver damage could be affected profoundly by the diet, a high calcium diet affording considerable protection.

Widmark (Hjort et al. [1939]) found that the ethyl alcohol level of the blood of fasting dogs was lower than it otherwise was when the fasting animals received various amino acids with the alcohol, by mouth. He also observed a similar effect when proteins or certain acids were given with the alcohol; water, fat, and carbohydrate were ineffective.

A notable increase in sensitivity of rabbits to cocaine was accomplished by Nedzel (1934) when the animals were placed on an acid-forming diet (urine reactions) over that found when they were living on an alkali-forming or mixed diet. He (1935) has described experiments which suggest that rabbits are more sensitive to ethyl hydrocupreine hydrochloride poisoning when on an acid-forming diet. In considering the influence of diet upon the action of phenobarbital sodium in rabbits, Nedzel (1937) found evidence that the animals on a diet producing an acid urine undergo longer general anesthesia than those on a mixed diet (urine nearly neutral).

Hjort, deBeer, and Fassett (1939) have studied the effect of diet in albino mice upon the anesthetic qualities of several hypnotics (unsymmetrical n-propyl-o-tolyl urea, ethyl-o-ethylphenyl urea, and sodium ethyl [1-methyl-butyl] barbiturate). Remarkable variations in sleeping time were elicited by altering the diets.

TABLE VI

DIET	NUMBER OF MICE USED	MEAN SLEEPING TIME (MINUTES)
1. Whole grain diet	30	85.6
2. Grain flour diet	59	93.2
3. Purina dog chow	30	19.3
4. High carbohydrate diet	57	48.5
5. High protein diet	57	34.9
6. Grain diet with cod-liver oil	58	81.4
7. Grain diet with cod-liver oil and ascorbic acid	58	91.5
8. Grain and milk diet	57	55.8

They were unable to determine the cause of these variations in sleeping time. Interestingly enough, they did not appear to be related to acid-forming or base-forming elements, for the diets used tended to be acid-forming. Reasons are presented why the variations cannot be explained on the basis of high protein or high carbohydrate contents. Whatever the explanation may be for the variations in sleeping time, the practical point to be gained from these studies is

that variations in diet of experimental animals may be responsible for great variations in sleeping time, hence the necessity for controlling this factor in anesthesia studies. Not only were significant differences obtained in the minimum hypnotic dose (unsymmetrical n-propyl-o-tolyl urea) but in the minimum lethal dose as well.

One cannot escape the obvious implication of the above studies that variations in diet may be responsible, at least in part, for the puzzling and at times dangerous variations in response of patients to the clinical use of barbiturates.

There is no need for reviewing at this time the great number of well-known studies on the influence of diet on the development of chloroform poisoning in animals subjected to anesthesia with that agent. The recent interesting studies of Ravdin and his associates will, however, be considered below.

Blackberg and Hrubetz (1936) have found, in a study of the factors which influence pentobarbital (nembutal) anesthesia, that glucose by vein does not materially shorten the duration of anesthesia, whereas fasting for twenty-four hours materially increases the period of anesthesia. No correlation between blood sugar levels and susceptibility could be demonstrated. The blood sugar level at the time of greatest depression from the agent continued at the initial level until the time of recovery, when a definite drop occurred.

Blackberg and Hrubetz (1937) report that fasting for twenty-four hours increases the susceptibility of rabbits to pentothal. The duration of anesthesia is lengthened. No correlation was found between the blood sugar level and the susceptibility to the drug.

One of the well-known hazards of the use of barbiturates is their variability of action. The factors underlying this variability are not at all clear. It is known that fasting increases susceptibility to barbiturate action, and so the findings of Hrubetz and Blackberg (1938) are of considerable interest. They found that, although animals (rabbits) deprived of food for twenty-four hours showed an increased susceptibility to the anesthetic, they could not correlate this with the blood sugar levels. Nembutal and amytal produce no change in blood sugar levels at the time of deep anesthesia. Phenobarbital causes none in the first hour. Pentothal and seconal bring about a rise in the first hour. In general, the agents produce a significant fall in blood sugar level at the time of recovery from anesthesia. Since lowering of the blood sugar level does not explain the increased drug effects, they investigated liver function and carbohydrate mobilization.

With each of the barbiturates studied (nembutal, pentothal, seconal, amytal, and phenobarbital) they found a marked depression in the glycogenolytic power of the liver as shown by the absence of or diminution in the rise in blood sugar after epinephrine. The short-acting

barbiturates are believed to be largely detoxified in the liver and accordingly might be expected to influence the glycogenolytic function of that organ; however, phenobarbital eliminated by the kidneys likewise depresses liver function. These findings strongly suggest that all barbiturates, however eliminated, produce a transient impairment of liver function.

Ravdin, Vars, Goldschmidt, and Klingensmith (1938) believe that the prolonged hyperglycemia observed following termination of chloroform anesthesia is due to damage of liver cells (dogs, white rats) by the anesthetic agent. Liver glycogen content was found to be reduced steadily during the anesthesia period. About 35 per cent of the liver glycogen was lost during a two-hour period of anesthesia; however, glycogen continues to disappear from the liver so that 94 per cent of it has been lost twenty-four hours after anesthetization. With the fall in liver glycogen concentration, the fatty acid concentration of the liver increases. When glucose is administered following anesthetization, a simultaneous increase in liver glycogen and liver fat occurs. This is evidence against the existence of a reciprocal relationship between these substances as reported by others.

The influence of foodstuffs upon the susceptibility of the liver to injury by chloroform and the probable mechanism of their action have been considered in rats by Goldschmidt, Vars, and Ravdin (1939). They find that the incidence and severity of damage to the hepatic cells increases progressively with an increase in the concentration of lipids in the liver. This is quite independent of the content of glycogen in the liver at the beginning of the anesthesia; but it may be modified by the protein content of the ration. The chief reason for the protection of the liver against injury, following a diet high in carbohydrate content, is probably the reduction in the lipid content of the liver which results from such a diet. Under certain circumstances, for example, inanition, the administration of carbohydrate may protect the liver by its protein-sparing action. Ravdin and his associates find no evidence that the depletion of hepatic glycogen by chloroform is associated with the metabolic requirements of the liver. They consider that this depletion is probably a manifestation of a effect of the toxic agent.

A high protein diet preceding chloroform anesthesia greatly reduces the incidence of hepatic cellular necrosis, even in livers which contain a high lipid content, and because of this, notwithstanding a severe attack by the chloroform.

Vars, Goldschmidt, and Ravdin (Ravdin [1939]) present further evidence that the high carbohydrate intake acts in several ways in protecting against chloroform poisoning:

1. Liver glycogen displaces liver fat. (Fat concentrates the anesthetic agent by absorption, and the agent produces necrosis by direct cellular damage.)

2. The high carbohydrate intake spares the reserve stores of protein in the liver. (These are important in protecting against hepatotoxins, such as chloroform.)

Adequate protein, as well as abundant carbohydrate, in the diet is important. Food by mouth is essential if intravenous glucose is to increase the quantity of carbohydrate stored in the liver, the authors state.

Liver Damage and Sleeping Time Under Barbiturates.—

Cameron (1939) recalls the work of Pratt and his associates (1932, 1933), finding that dogs given nembutal twenty-four hours after prolonged chloroform anesthesia sleep much longer than "normal" animals. No such effect was found for barbital. Koppanyi and his associates (1936) confirmed this work in cats and dogs. These workers, however, found prolonged sleep with barbital. They suggested that chloroform injures the nerve cells, making them more susceptible to the barbiturates. Cameron and deSaram (1939) produced liver damage by means of carbon tetrachloride. Following this, nembutal and evipan were found to produce abnormally prolonged sleeping times, although in the case of the slow-acting agents, medinal and luminal, no prolongation was observed.

Progressive liver damage was produced in rats by giving twice-weekly doses of carbon tetrachloride subcutaneously, with the results shown in Table VII:

TABLE VII

DURATION OF LIVER DAMAGE	NUMBER OF RATS	MEAN DURATION OF SLEEP IN MINUTES AFTER STANDARD DOSE OF NEMBUTAL*	MORTALITY FOLLOWING STANDARD DOSE OF NEMBUTAL
Normal	55	102 ± 4	0
One month CCl_4 intoxication	20	148 ± 14	12.5%
Two months CCl_4 intoxication	18	208 ± 10	28.0%
Three months CCl_4 intoxication	12	249 ± 22	58.0%

*Forty mg. per kilogram of body weight, given subcutaneously.

After one month of CCl_4 intoxication, the liver shows only very slight alteration either grossly or microscopically, yet a significant prolongation of sleeping time occurs, and lethal effects occur with a dose below the normal minimum lethal dose.

In other experiments they found that chilling increased the mortality.

Some Examples of the Use of Anesthetic Agents in Studying Physiologic Processes.—

Acquired Resistances of Fixed Tissue Cells: MacNider (1938) reviews his work extending over thirty years on the acquired resistance of fixed cells (liver, kidney) that develops as a process of cell metaplasia secondary to tissue injury (uranium, chloroform). These studies

are of interest here simply as an example of how anesthetics, even their toxic effects, can be utilized in unravelling the processes of physiology and pathology.

Blood Clotting: Smith, Warner, and Brinkhous (1937) present another example of the use of an anesthetic agent (chloroform) in the study of liver function. In severe liver damage by chloroform, disturbance of blood clotting occurs. Clots can form, but they are flabby and ineffectual in controlling hemorrhage from minor incisions. The bleeding tendency is due to a deficiency in fibrinogen and also to a great fall in plasma prothrombin. Smith and his associates (loc. cit.) have demonstrated (in dogs) that the prothrombin is more labile than the fibrinogen. When the chloroform dosage is small, the prothrombin level falls much more markedly than the fibrinogen level. By using repeated small doses of chloroform, these two clotting factors can be dissociated, the fibrinogen level remaining unaffected, while a great fall in the prothrombin level occurs. The relation of liver injury to the plasma prothrombin level demonstrates that the liver is concerned in the manufacture of prothrombin. Chloroform damage appears to interfere more easily with prothrombin formation than with fibrinogen formation.

Renal Function.—

The effects of the common anesthetic agents on normal kidney function have been studied on several occasions. In this regard, the recent paper of Orth and Stutzman (1938) is of considerable interest. Since urea is the chief product of excretion in the urine and since both tubules and glomeruli are involved in filtration and reabsorption, urea clearance determination would appear to give an index of the action of anesthetic agents on the kidneys if damage occurred. It is well known that slight fluctuations in clearance values may occur and represent normal variation in kidney function. Sixty- to seventy-five-minute periods of "surgical" anesthesia with cyclopropane, ether, or chloroform were carried out in dogs at about weekly intervals for many weeks. The results indicate that none of the three anesthetic agents studied interferes with kidney function, as determined by urea clearance. Repeated collections of twenty-four-hour urine samples following each anesthetic agent also showed normal volumes. Microscopic examination showed "slight casts, leucocytes, and occasional erythrocytes." A slight albuminuria was present after ether but cleared within a few days. The authors did not encounter this after cyclopropane or chloroform. They have never found glycosuria.

It has been shown by a number of workers that the rate of secretion of the urine is diminished under sodium isoamylethyl barbiturate. It has also been shown that under this agent dilution of the blood occurs. Gouaux and his co-workers (1937) have studied the effect of this anesthetic agent in fifty dogs, and they find that there is no serious interference with kidney function, as measured by the urea excretion.

Smith, Rovenstine, and their associates (1939) have studied the circulation of the kidney under spinal anesthesia in twenty-one unoperated subjects. Anesthesia to levels above those at which the efferent sympathetic paths to the kidneys emerge from the cord does not produce renal hyperemia, nor any consistent effect upon renal circulation. They conclude "that the tone of the renal arterioles is normally maintained by autonomous, intrinsic activity of the peripheral vascular apparatus and is not dependent upon tonic activity of the central nervous system."

In 1935, Zilva presented evidence that, when compounds of the ascorbic acid series were injected into guinea pigs previously depleted of vitamin C, only the antiscorbutically active members were "fixed" by their tissues. There was, furthermore, some indication that a quantitative relationship existed between degree of activity and quantity "fixed" by the tissues. The amounts of the compounds excreted by the kidneys varied inversely with their antiscorbutic activity. When ether anesthesia was used to facilitate the intravenous injection, the quantity of l-ascorbic acid excreted in the urine increased (doubled) over that excreted in the urine when no anesthesia or procaine local anesthesia was employed. When the several compounds were considered, the influence of the general anesthesia became less as the activity of the antiscorbutic compound diminished.

Kolb and Langworthy (1938) have carried out a comparative study of the effects of barbiturates, ether, and bulbocapnine upon micturition.

Suprarenals.—

Knoefel (1936) has pointed out that many of the undesirable side effects of ether and chloroform anesthesia resemble effects produced by epinephrine and has suggested that a major cause of these side effects is an increased output of adrenin from the suprarenals as a result of stimulation of the hypothalamic "sympathetic center" and increased stimuli through the thoracolumbar system.

Emerson (1938) has pointed out that test of Knoefel's hypothesis should be based upon direct examination of the adrenin content of the suprarenals rather than upon indirect biochemical evidence. Emerson has made such a test and reports (1938) a significant decrease in the amount of adrenin found in the suprarenals of cats anesthetized with ether for thirty minutes, but this was not so after divinyl ether. The decrease did not occur under ether if barbiturate premedication was used.

An increased outpouring of adrenin during anesthesia may be due to (1) excitement during induction or recovery or (2) continued stimulation of the "sympathetic center" or the splanchnics during deep anesthesia. It is possible, as Emerson recognizes, that his results could be criticized justifiably on the basis that longer, stormier inductions under ether than under divinyl ether account for the findings. He attempted to correct for this by the deliberate use of slow inductions under divinyl ether.

Skeletal Muscle Tonus.—

Muscle tonus is a slight elastic pull of muscles which, it has been suggested, is influenced to some extent via the sympathetic nervous system; however, the chief impulses responsible for it come through the motor nerves which control active movements. Muscular tonus is under the active control of the motor centers in the spinal cord. These centers are influenced by reflexes from the skin and muscles and by the higher centers. Oxygen and CO_2 contents of the blood also greatly affect tonus.

Strychnine increases the activity of the spinal nerve centers and increases tonus. Ether (early) increases muscular tonus. Henderson (1937) explains this by saying that the inhibiting influence of higher centers is eliminated and the lower centers become more active. In full anesthesia the activity of the motor centers themselves is diminished, and tonus is lessened or abolished. The muscles relax and become flaccid.

The above is widely accepted. Henderson reports:

1. Tonus induces a pressure within a muscle.
2. This pressure forces the blood onward toward the heart. With low tonus the blood tends to stagnate in the capillaries. With high tonus the flow onward is promoted.

He attributes to low muscle tonus postoperative pulmonary complications (high diaphragm, etc.) as well as shock.

SPECIAL FIELDS

Peridural Anesthesia.—

Tuohy (1938) describes how Pagés in 1921 and Dogliotti in 1933 independently worked out a method of producing segmental or localized anesthesia by injecting a local anesthetic agent into the peridural space. In this space the anesthetic acts upon extradural portions of the spinal nerves, upon the spinal ganglia, and upon paravertebral sympathetic nerves. Usually from 30 to 40 c.c. of a 2 per cent procaine hydrochloride solution are injected; segmental peridural anesthesia then lasts from one to two hours. The chief advantages of this method, as stated by Dogliotti (summarized from Tuohy), are that (1) there is no danger of diffusion of the anesthetic toward bulbar centers; (2) anesthesia is reduced to a very limited segment of the body; (3) there is less fall in blood pressure than that occasioned by subarachnoid injection; (4) there is less nausea and vomiting than occurs under spinal anesthesia; (5) there is an incidence of "lumbar puncture headache" of less than 1 per cent; (6) in debilitated patients a greater margin of safety is obtained than with subarachnoid block.

As disadvantages, Tuohy lists failure to obtain adequate anesthesia in the proper region in some cases and considerable delay in obtaining anesthesia. Perhaps Tuohy considered it too obvious to mention in the outline referred to, but it seems to this reviewer that one should include the hazard of the needle's accidentally puncturing the dura

and arachnoid. After the injection has been well started, it is difficult, if not impossible, to determine whether one is in the peri- or subdural (subarachnoid) space; the two chief tests which indicate the peridural space can no longer be elicited; the negative pressure is no longer present and injected fluid can be aspirated. More than one able anesthetist can testify that this hazard is a practical one. Such large quantities of procaine are used in the peridural technique that, when an accident occurs and these are injected into the subarachnoid space, an extremely serious situation results.

Odom (1936) uses pontocaine and procaine combined in peridural anesthesia, obtaining anesthesia which lasts from one and one-half to two hours. He has described in detail the anatomic background and the technique employed to produce peridural anesthesia.

The Rectal Use of Evipal.—

The rectal use of evipal has been recommended by a surprisingly great number of writers: Gwathmey (1936, 1937, 1939), McNellis (1937), Hogan (1937), Soresi (1937), Harrison and Dunphy (1938), Meana and d'Accinni (1938), Weinstein (1938), and Jones (1938).

There are two main routes of administration for nonvolatile agents for general anesthesia—the veins and the rectum. Some agents, such as avertin, can be introduced only through the rectum. But in the case of the barbiturates, many can be introduced directly into the blood stream. The recommendations of these papers, that the barbiturates be introduced rectally, raise the question of the relative controllability of these two routes of administration.

Several points are pertinent to such a consideration:

1. Once an agent is placed in the rectum it is nearly impossible to recover it after it begins to exert its normal action or to give toxic effects. While high colonic enemas may be tried in an endeavor to wash it out, the fact is that such action may sweep the offending agent higher in the bowel and allow even more rapid absorption with greater toxic effects to follow.

2. Even though a solution of given volume may be injected into the rectum at a standard speed, it is impossible to say to what height it will travel up the bowel. There are a number of reasons for this. There is no need to point out how uncertain cleansing of the bowel may be as a result of routine enemas. The height to which an anesthetic agent will rise on being placed in the rectum is determined in large part by the fecal content of the bowel. Other factors active in regulating height (and impossible of accurate evaluation) are tone of the bowel, peristalsis, and anatomic anomalies. Using a dilute barium solution under exactly the same conditions as avertin is used, Sebening found on roentgenographic examination that in two patients the entire colon including the cecum was filled; in two the midascending colon was reached; in four the hepatic flexure was attained; and in

four the midtransverse colon, in seven the splenic flexure, and in one patient only the rectosigmoid junction was reached.

3. It is well known that the toxicity of the nonvolatile anesthetic agents depends to a great degree upon their rate of absorption. With some of the agents, as with sodium barbital, while the blood level is rising as a result of absorption, it may be counterbalanced by excretion through the kidney and a safe blood level may thus be maintained. In other cases, as with the fast-acting barbiturate, evipal, a safe blood level depends in great part upon liver destruction concomitant with absorption. An abnormally rapid rise in the absorption rate, however, easily upsets the balance experience has taught is safe, and serious toxic effects follow. The higher agents travel up the bowel, the more rapidly they will be absorbed.

4. The following statement, then, seems to be a reasonable one. If we cannot efficiently remove an agent once it is placed in the rectum, if we cannot control the height to which a solution injected into the bowel will rise, then it follows that we cannot control the rate of absorption. In other words, we cannot accurately control the toxicity of nonvolatile agents used rectally. If an agent can be used intravenously there is no reason to resort to the relatively inaccurate and unsafe rectal route. One wonders if the defenders of the rectal route of administration of the barbiturates are prepared to claim that there is any magic in the *route* of absorption. The implication is inescapable in some of the papers referred to that rectal administration prolongs the action of the drug! The rate of administration can be precisely controlled through intravenous drip methods, and if toxic signs appear, the administration can be curtailed immediately. It seems evident that such a method is more desirable than one which cannot be controlled precisely. (Beecher, 1939.)

Also pertinent to this review is the following discussion of the article by Werner, Pratt, and Tatum (1937).

When each of several agents is destroyed by the body at a differing rate, route of administration must loom large in considering dosage. For example, these workers have shown that the order of decreasing toxicity of a number of barbiturates administered by vein is not the same as the order of decreasing toxicity by rectum or by gastric tube.

When the minimum lethal dose ratio (intravenous to oral administration, I:O) is compared for a number of barbiturates with the duration of action, it also becomes plain that a high M.L.D. ratio is associated with brief action when administered intravenously. To put it another way, as duration of action increases from one compound to another, the toxicity ratio decreases. A high ratio (I:O) indicates that detoxication occurs rapidly. The studies just described were based upon values found in rabbits, and they cannot be casually transferred to man. It is likely, however, that the principle would apply

TABLE VIII

COMPARISON OF THE M.L.D. RATIO TO DURATION OF ACTION

AGENT	M.L.D. RATIO* 1:0	DURATION IN MINUTES OF ACTION (60% M.L.D. INTRAVENOUSLY)
Pentothal	1:17	28
Evipal	1:15	42
Thio analg. of amytal	1:15	45
Alkyl secondary—butyl thiobarbituric acid	1:8	97
Nembutal	1:6	130

M.L.D. = dosage of drug in mg. per kg. which kills 50 per cent of the animals (rabbits).

*In round numbers (Werner et al. [1937]).

in both cases, and one would expect that, if the very short-acting barbiturates are to be used orally, the variation between satisfactory intravenous and oral doses will be even greater than when the longer-acting agents are used.

Doses of various barbiturates used for production of similar periods of narcosis by oral administration must be inversely proportional to the duration of action obtained on intravenous use. This indicates that certain hazards will be introduced if any attempt is made to employ the very fast-acting barbiturates by any route which allows the situation to be complicated by the absorption factor, as it is in oral or rectal administration. The very fast-acting barbiturates are destroyed so rapidly in the body that, if they be used orally or rectally, the time required for absorption delays entry so that relatively large doses must be used. Individual variations in absorption rate render such practices dangerous. So it seems doubtful if the very fast-acting barbiturates can ever be used safely except by vein; at least, the slow routes of absorption are unpromising as long as the toxicity of these substances remains as high as it is. The very short-acting barbiturates when used by vein should, other things being equal, be safer for intravenous use than are the slower-acting ones. This is so because the very fast-acting agents are characterized by rapid induction, a rapid appearance of the maximum effect, and a rapid destruction. This permits a more precise control than is obtained with the slower-acting barbiturates.

It is interesting to observe that the ratio of the minimum lethal dose to the minimum hypnotic dose is similar for each of the five barbiturates studied here. The ratio is of the order of 5.

Anesthesia for Thoracic Surgery.—

Eversole and Overholt (1936) have pointed out that patients who must undergo thoracic surgery are often poor risks from the anesthetist's point of view. Suffering from protracted illness and long periods in bed, they may be in poor general condition. This group tolerates even slight

degrees of anoxia poorly. The absorptive surface of the lungs is reduced by the lesion. Abnormal quantities of mucus and pathologic secretions bathe the tracheobronchial tree. Coughing may be frequent. When the patient is placed upon the operating table, the good lung is down and its functioning volume is reduced by the weight of mediastinal organs and by a high diaphragm on the underside. It is cramped by the position of the patient and by supporting pillows.

It is generally agreed that local or regional anesthesia is satisfactory for drainage of empyema, thoracotomy for lung abscess, and for closed pneumolysis.

A detailed list of advantages and disadvantages of common agents is presented.

Beecher (1938) has considered the hazards to be overcome in determining the best choice of anesthetic agent and of anesthesia procedure in the difficult group of cases requiring surgery through the open chest. The chief hazards which the plan of anesthesia should be designed to overcome are: (1) obstructing secretions and blood in the airway; (2) troublesome reflexes, including cough; and (3) anoxia and circulatory strain.

Secretions or foreign material in the airway not only obstruct, but when sprayed over the good lung tissue may cause pneumonitis. Secretions and blood must be controlled, and they can be controlled through postural drainage before and during operation. The operation is carried out with the patient in the head-down position. Aspiration of the bronchi, as indicated throughout the operation, can also control secretions and blood. This necessitates the use of an intratracheal tube which should be inserted as soon as possible after induction of anesthesia. Cocainization of the pharynx is unnecessary for this procedure in most cases and adds to the hazards. The insertion of an intratracheal tube under local anesthesia (before general anesthesia is induced) may be justified if the sputum is very profuse. At certain periods during open chest operations, routine aspiration through the intratracheal tube should be carried out whether or not secretions can be heard in the airway. Notably, this should be done when the patient is turned on his side following induction and intubation, just after the pleura is opened, when the diseased lung tissue is mobilized, when the tourniquet about the lung stump is released, and at the end of operation before removal of the intratracheal tube. Finally, the liberal use of atropine in gr. $\frac{1}{100}$ to gr. $\frac{1}{75}$ doses given subcutaneously will help minimize the formation of troublesome secretions in the airway.

Troublesome Reflexes: Cough is normally initiated by local irritation in the air passages. The reflex can be set up by surgical irritation of the afferent vagal fibers in the pleura. Efficient cough requires a closed glottis and intact chest wall so that intrathoracic pressure may be built up. Efficient cough is impossible during open chest operations, not only

because of the impossibility of building up a relatively high positive pressure, but also because of the unfavorable position of the patient during this type of surgery. It has long been recognized that cough has a spreading action as well as expulsive action. When a person attempts to cough with an open chest, he produces a sudden herniation of the lung through the orifice; coincident with this there may be a spread throughout all parts of the lung of infectious or irritating material that may be in the airway. Since cough has a spreading action, it is of great importance to keep the airway free of infectious material. Cough during thoracic surgery dangerously increases the technical difficulties of the procedures undertaken. It is a mistake to preserve the cough reflex in this group of cases during operation. The anesthetist, not the patient, should assume the responsibility for maintaining free air passages.

Reflexes producing troublesome consequences are particularly likely to be set up by surgery at the hilum. Vagal stimulation occurs, leading to an irregular, jerky type of respiration interspersed with sudden periods of apnea, and the heart rate is slowed.

These troublesome reflexes can be minimized by the use of atropin, since this drug frees the vagus. At times it will be necessary to inject procaine directly into the vagus, as well as beneath the parietal pleura over an area about 15 cm. in diameter surrounding the pleura. Occasionally it will be necessary to eliminate the movements of the diaphragm on the side of the operation by injection of procaine directly into the phrenic nerve.

Anoxia and Circulatory Strain: The body's normal oxygen supply is hindered by obstruction of the airway and by the open pleura. The latter allows, as a result of the action of atmospheric pressure in the open chest and the respiratory movements, swinging of the mediastinum. Not only does this limit the aeration of the contralateral lung, but it gives rise to reflexes which probably are responsible for a fall in blood pressure. The open pleura interferes, then, not only with the intake of oxygen but with its distribution as well.

Several factors operate to reduce the circulating blood volume. In warm weather sweat loss is a factor. Pleural and mediastinal reflexes are important in the reduction of the volume of circulating blood. Also important are the circumstances which tend to produce shock, such as prolonged surgery and chilling. The heart is subject to great strain due both to direct pressure during the surgical manipulation and to anoxia. Generally this circulatory strain is latent and becomes apparent only if the patient is improperly handled at the end of the operation, as, for example, in careless, abrupt changes of position.

Anoxia produced as described above can be combatted in a number of ways. Atropin reduces the troublesome reflexes and diminishes the quantity of mucus and saliva formed. A closed anesthesia system and an intratracheal tube allow the administration of a constant high per-

centage of oxygen and the use of positive pressure anesthesia whenever it is needed to inflate collapsed portions of the lung, to restore or maintain a good blood color, or to aid in stabilizing the mediastinum. The head-down position promotes drainage; it perhaps minimizes the possibility of cerebral emboli, and it aids in maintaining an abundant blood supply to the vital centers. Intravenous fluids, blood in particular, sustain the circulating blood volume notwithstanding the tendency to a decrease in it during surgery in the open chest. Blood transfusion also counteracts the copious postoperative weeping of the pleura, with the consequent loss of, in many cases, 500 c.c. or more of blood plasma.

Choice of an Anesthetic Agent: The choice is considerably limited by the exacting requirements of this group of cases, as outlined above. Ether seems to fit the requirements best, because of the high oxygen percentage one can use with it, the tolerance of the circulatory system for it, the low toxicity of the agent, and, finally, its low mortality. The use of avertin for these cases is not desirable because of its depressant action on the respiration and circulation and its high mortality. Cyclopropane cannot be unreservedly accepted, chiefly because of its to date inadequately evaluated toxic cardiac effects. Spinal anesthesia, preferred by a few intrepid surgeons, violates all of the requirements outlined at the beginning of this paper and is not suitable for this group of cases.

Various Agents: Rovenstine (1936) describes the use of intrabronchial tubes for open chest surgery.

Coryllos and Bass (1939) describe the use of several anesthetic agents in 1,370 cases undergoing thoracic surgery, chiefly thoracoplasties. Three hundred cyclopropane anesthesias were administered to this group. They report that "in many cases there was a marked drop in blood pressure with coincident shock as soon as the mask was removed at the end of operation." They believe that bleeding is increased under this agent over that of other agents. The most arresting information contained in their paper is the report that they encountered five cases of generalized convulsions and three others with localized muscular twitchings in 300 cyclopropane anesthesias for thoracic surgery. These led to death in three cases. In comparison with this, they refer to 1,600 previous thoracic cases, with only one convulsion. In the 300 cases under cyclopropane, ten died twenty-four hours or less after operation, one patient dying during induction.

Brown (1938) states that ether is contraindicated for use in pulmonary tuberculosis. His statement is based upon its use in ten operations for treatment of pulmonary tuberculosis. The reviewer takes strong exception to this statement, based upon a five-year experience at the Massachusetts General Hospital where several hundred thoracoplasties have been carried out under ether anesthesia, with exceptionally satisfactory results. This material is being prepared in detail for publication.

Two hundred and twenty-six patients (Coryllos and Bass [1939]) received avertin (average dose, 60 to 80 mg./kg.), with two deaths directly attributable to the avertin, according to the authors. Four deaths occurred the day of operation in this group.

The use of evipal anesthesia in 200 thoracoplasties is described by Coryllos and Bass (1936). In these 200 cases the average initial systolic pressure was 123 mm. Hg, and the average minimal systolic pressure was 76 mm. Hg. In thirty patients the initial fall in blood pressure was so great that the systolic pressure could not be elicited at the arm. The authors refer to the "favorable results" of this type of anesthesia for thoracoplasty, higher praise than most anesthetists would be willing to grant.

Gurd, Vineberg, and Bourne (1938, 1939) describe their experiences with the use of spinal anesthesia for thoracoplasty. They have treated forty-two patients under spinal anesthesia. They have had two deaths in the operating room and three other bad scares, all of which are attributed to the anesthesia. It is surprising to find, notwithstanding this experience, that the general tone of the paper gives favorable consideration to this type of anesthesia for these cases. It is also surprising to find the statement that they have not noted phrenic root paralysis with interference with functioning of the diaphragm, surprising when the paper mentions two deaths and three bad scares. The only case described in detail is one typical of this latter group; respiratory and cardiac failure both occurred here. Also, "less bleeding" accounted for by a drop in blood pressure would scarcely seem to be an advantage. This paper hardly raises the reviewer's enthusiasm for spinal anesthesia for thoracoplasty.

Newton (1935) has used spinal anesthesia in twenty-eight consecutive thoracoplasty operations. He advises its use in selected cases, in patients "with mental poise." He states that in patients under spinal anesthesia he sees less shock than in patients under nitrous oxide, local and avertin. Possibly so, but neither of these choices seems desirable to this reviewer.

Lundy, Tuohy, Adams, and Mousel (1939) advocate the use of spinal anesthesia for lobectomy and total pneumonectomy because "the patient is able to cough and raise mucus." They also claim that its use reduces the danger of postoperative pneumonia or infection of the good lung with mucus from the affected side. The reviewer disagrees with this. An efficient expulsive type of cough is not possible with the chest wall open. A cough with the chest open, when the airway contains irritating, infectious material, is likely to spread the sputum and it increases the danger of postoperative pneumonitis.

Burnett (1937) describes the use of local anesthesia for a one-stage pneumonectomy.

A good deal has been written (cf. Burford [1938]) about sudden massive collapse of one or both lungs during anesthesia, followed by

death of the patient. Naturally, death is to be expected if both lungs remain collapsed. It is difficult for this reviewer to accept the often-made statement that the sudden massive collapse of one lung is to be followed by death. In several hundred open chest explorations at the Massachusetts General Hospital the sudden massive collapse of one lung has not resulted in harm, and this with the activity of the good lung hampered by being on the underside. No portion of lung which is to be saved is allowed to remain collapsed during operation for more than about fifteen minutes, for if this time is exceeded the collapsed portion may become seriously edematous. Edema has been observed to develop while such collapsed portions were watched.

The breathing of an abnormally high percentage of oxygen during anesthesia will lead to collapse of peripheral portions of lung in unventilated regions. During periods of hypoventilation the proportion of unventilated and probably collapsed regions may assume important proportions. Accordingly, it seems desirable to use a little positive pressure—not more than 8 or 10 cm. H_2O for two or three minutes every fifteen minutes—when using a high concentration of oxygen in the gases inspired. This, of course, will not overcome the collapse due to plugged bronchi. Bronchial aspiration or bronchoscopy may be required to overcome this if moving the patient or coughing is not adequate at the end of operation. Others have attacked the problem by adding inert gases, such as nitrogen or helium (loc. cit.). In unpublished experiments in dogs Beecher found that only a few breaths of room air were sufficient to eliminate the danger of pulmonary collapse when the respiration was checked at about the time the animals were breathing high oxygen mixtures.

Anesthesia for Diabetic Patients.—

Hale and Tovell (1938), in considering the choice of anesthetic agents and methods for diabetic patients, conclude on the basis of observations of 279 anesthesias in 244 patients that the common anesthetic agents may properly be used in diabetic patients, providing the diabetes is carefully controlled pre- and postoperatively, and providing long surgical procedures or large quantities of ether are avoided. It is very important to avoid anoxia.

Wilcox and Tovell (1939) have more recently considered this subject.

Firor, Lamont, and Shumacker (1940), in a study of the cause of death in tetanus, observed in dogs with general tetanus that the injection of a usually safe dose of nembutal would kill the animal in a short time. They also observed that, when tetanus toxin was given intravenously, the administration of enough nembutal or avertin to stop convulsions shortened life. While such observations must obviously be transferred to man only with great caution, Firor's reports offer a real challenge to a heretofore accepted part of the therapy

of tetanus in man. However, statistical analysis of the data presented indicates that the differences between the control and the anesthesia groups are not significant, except in one (out of four) cases in which the differences shown are possibly significant but not clearly so. More data might substantiate Firor's statements; those presented fail to do so.

Anesthesia in the Treatment of Tetanus.—

Chia (1938) has successfully treated a case of advanced tetanus with, among other things (wound surgically cleaned, antitoxin, hydrogen peroxide in the wound, etc.), avertin anesthesia (four rectal injections on four successive days, 80 mg. per kg. at first, then 60 mg./kg.). Potassium bromide and chloral were also used.

O'Farrell (1938) describes one patient with advanced tetanus who recovered following prolonged pentobarbital anesthesia (as well as specific treatment).

HAZARDS AND COMPLICATIONS OF ANESTHESIA

Reports of Postoperative Pulmonary Complications.—

If one were to judge from the many papers written on the subject, it would seem that a major occupation of anesthetists was the compilation of statistical studies regarding the incidence of postoperative pulmonary complications under various agents. The chief interest of such studies appears to be centered in demonstrating that the newest agent occasions the lowest number of postoperative pulmonary complications in comparison with the longer used agents. One's faith in the value of such studies is considerably weakened by finding that what purport to be statistical analyses have in all but a very few cases failed to take into account the most rudimentary requirements of statistical analysis. The casualness with which many writers undertake statistical analyses does not alter the fact that such matters are involved, time-consuming, and utterly valueless unless the fundamental laws of statistics are observed. Unhappily, statisticians and their statistics are looked upon with suspicion by the rest of the world. To be sure, statistical methods are not a substitute for common sense; on the other hand, some use of such methods is necessary if common sense is to be preserved in the handling of quantities of data.

Whenever this reviewer is confronted with a new series of data which tends to show that one anesthetic agent is followed by fewer postoperative pulmonary complications than another, several questions come to mind. If the anesthetic agent is of considerable importance in this regard, why is it that men are found to have many more of these complications than women? The ratio varies from study to study, but the incidence is usually stated as from two to four times greater in men than in women. Every one is agreed, it seems, that upper abdominal operations are followed by a very much higher incidence of postoperative pulmonary complication than are lower

abdominal operations. If the anesthetic agent plays any considerable role, why is this so? The condition and sex of the patient, the duration and depth of the anesthesia, and the operation have all been shown to be important factors. Surprisingly often, observers have reported the same general incidence of complications following a given operation (with like conditions) under general, local, or spinal anesthesia. If the anesthetic agent itself is of much importance, these studies must be in error. Both points of view cannot be correct. Where the truth lies is uncertain. It will scarcely be revealed by the typical study of the matter to be found in the literature.

As far as pulmonary complications are concerned, comparison of postoperative results in one hospital with those in another is a hazardous and uncertain procedure of highly questionable value. Certain it is that none but the most remarkable difference needs cause any comment. Instructive comparisons are rare. In the case of postoperative pulmonary complications, the general experience has been that, when complications are looked for in succeeding years, the number found is directly proportional to the interest and duration of the study. Type of patients, housing conditions, and the abilities of the surgeon and anesthetist all vary, so that comparison of results is probably of little value.

Dr. Waters (1936) wisely summed up the matter when he said, "I think the teaching usefulness of records is to the man who keeps the records rather than to others in general."

It is sometimes stated that the duration of an operative procedure greatly influences the incidence of postoperative pulmonary complications, and yet there are many reasons for questioning the role of duration per se. However, prolongation of deep anesthesia, like other procedures which greatly tax the patient, is probably important in increasing the incidence. For example, few major respiratory complications occur following obstetric and gynecologic operations. Many gynecologic operations last a very long time. It seems nearly impossible to this reviewer to dissociate the factors which require the long operation, the blood loss incidental to it, the traumatic reflexes, the tissue damage which may accompany operation, the prolonged anesthesia, and often the long operations mean the surgeon was in trouble, and many other factors, all of which probably play a part in determining the average higher incidence of postoperative pulmonary complications following long operations. Duration of anesthesia itself may not be of so much importance as other specific factors which operate during the time recorded. Such data may give a false impression of the advantages to be gained by speed. The uniformly longest operations at the Massachusetts General Hospital are those that involve surgery in the open chest. After several hundred such operations (most carried out under ether anesthesia), it can be said

that the type of postoperative pulmonary complications found after gastric surgery, for example, are very unusual in this group. Emphasis on duration of anesthesia may in the future be shown to be justified; at the present time emphasis on other factors would seem to be equally, or even more, important.

Convulsions and Brain Damage During Anesthesia.—

Convulsions: In the past dozen years or so, increasing reports of convulsions during anesthesia have been appearing in the literature. This certainly does not mean that the phenomenon was unknown before 1927, when the first reports were made, but it is one more example of the value of calling attention to a morbid process: once described, many reports appear. A telling commentary on the confused state of our knowledge of this occurrence is offered by a glance at the numerous and conflicting suggestions as to etiology (cf. Beecher, 1938). Nearly as many suggestions as to cause are offered as there are writers on the subject. Most of the papers are based upon speculation. Their value lies chiefly in their case reports, for, in viewing these reports as a whole, certain fairly constant features stand out. These offer a working description, as far as it goes, of the phenomena. A typical convulsion is described as usually starting with twitchings of the face. These quickly spread and soon involve the entire body in clonic convulsions which last from a few minutes to several hours. In the latter case they generally terminate in exhaustion, circulatory failure, and death. Children or young adults appear to be most often attacked. The case record often contains the statement that respiratory difficulties have preceded the onset of the process. Respiratory failure may occur during the convulsions.

Lundy (1937) has tabulated 144 cases, chiefly from the literature. It is evident that convulsions occur under several anesthetic agents. The term "ether convulsions" is misleading.

Brief references to a number of other recent convulsions during anesthesia follow. Chadwick (1936) refers to a case of "ether convulsions" successfully treated by intravenous evipal, as do Dodd (1937) and Taylor and Goldman (1938). Hunt mentions (1938) evipal in the control of convulsions from novocain. Shackleton (1937) reports two cases of convulsions during anesthesia, an ethyl chloride-ether sequence. Mennell (1937) reports "ether convulsions" occurring twice in the same patient. Human (1937) reports a convulsion during nitrous oxide-ether anesthesia. Cartwright (1937) discusses muscular twitches during anesthesia as a result of anoxia under nitrous oxide and other agents, and as a result of poor muscular relaxation with muscles under tension, and finally discusses "ether convulsions." He reports nine cases occurring under several agents. The temperatures rose to 109° F. Daly (1937) reports two "ether convulsions." Thierry (1938) has collected a number of anesthesia convulsion cases from

the literature and has presented one of her own. Dodd (1939) thinks atropin responsible for "ether convulsions," reporting four cases. Gitlin (1938) reports a convulsion in a patient under nitrous oxide-ether anesthesia. An "ether convulsion" treated with calcium is described by Steel (1939). He also administered in therapy of the convulsion 35 per cent CO_2, later reduced to 17 per cent. There was recovery notwithstanding the high CO_2 inspired. Smith (1938) has attempted to show that a variety of complications during and after operation, including "late ether convulsions," may arise through derangement of the heat-regulating mechanism of the body, occasioned by overheating. He reports three cases of convulsions during anesthesia. Postconvulsive temperatures are given. Pinkerton (1938) reports one case of convulsions during anesthesia, an ethyl chloride-ether sequence. He reports postconvulsion rise in temperature, but the temperature had been elevated preoperatively.

Bradshaw (1939) reports a convulsion during anesthesia and includes data on ether kept and analyzed at weekly periods for a year. Tests for aldehyde, peroxide, and acid were made during this period. Only one sample showed a positive test (aldehyde), and that after ten months.

Griffith (1938) reports a convulsion during cyclopropane anesthesia. The convulsion appeared forty minutes after nasal packs soaked in nupercaine had been inserted and may have been due to this agent. The convulsion was controlled by intravenous sodium amytal.

One convulsion during cyclopropane anesthesia has occurred at the Massachusetts General Hospital. This was checked by intravenous sodium phenobarbital. (See also the case of Gebauer and Coleman [1938], referred to below.)

The extraordinary results of Coryllos and Bass (1939) are arresting. They encountered five cases of generalized convulsions and three others with localized muscular twitchings in 300 cyclopropane anesthesias for thoracic surgery. These convulsions were followed by death in three cases. In comparison with this, they refer to 1,600 previous thoracic cases under other anesthetics with only one convulsion.

Encephalopathy: Steegman (1939) reports four cases of encephalopathy following anesthesia, two after nitrous oxide, one after avertin, and one after cyclopropane, previously reported elsewhere. The cyclopropane case (Gebauer and Coleman [1938]) was that of a young woman who underwent a thoracoplasty for pulmonary tuberculosis. She was cyanotic following the operation, not during it. Convulsions appeared thirty-six hours postoperatively. She had a hyperthermia and at post mortem exhibited acute ulceration of the urinary bladder, acute hemorrhagic erosion of the gastric mucosa, and fatty infiltration of the myocardium. The brain was swollen.

The damage to the brain in the four cases appeared to be due to nerve cell deprivation of oxygen.

Henson (1937) refers to a delayed depression which resulted in death following the use of cyclopropane for a herniorrhaphy.

Lowenberg and Zbinden (1938) report further cases of brain damage under nitrous oxide anesthesia. They continue to attribute the damage found to a specific toxicity of nitrous oxide rather than to accompanying anoxia, and their arguments for this continue to be unconvincing to this reviewer.

Considerable debate has occurred as to whether the brain damage sometimes found after nitrous oxide administration is in truth due to accompanying anoxia or to a specific toxicity of the anesthetic agent. Pertinent here is a brief comparison of the effects of nitrous oxide and a simple asphyxial gas like nitrogen (Courville, 1938): (1) Under nitrous oxide the pulse is more rapid (the cardioinhibitory mechanism is less effective); (2) convulsive movements are less apparent under nitrous oxide, perhaps as a result of depression of motor nerve cells; (3) respiration fails sooner under the anesthetic agent, due to a specific depressant action on the respiratory center. Nitrous oxide produces depressant effects which disappear when nitrogen is substituted for it. Unquestionably, nitrous oxide has a true anesthetic effect. It is well known that true nitrous oxide anesthesia can be produced in many cases only at the lower limit of adequate oxygen supply. That this limit is often exceeded is demonstrated by the frequency with which cyanosis appears before true anesthesia can be produced. The zone under consideration is a borderline one, and it is accordingly difficult to reach a reasonably certain conclusion as to whether specific action of the nitrous oxide or asphyxia is responsible for the accidents reported. The evidence appears, however, to incriminate the latter. Narcotics do not produce structural changes in nerve fibers or interstitial elements; on the other hand, any or all structures show morphologic change following asphyxia. The similarity of the lesions found (including nerve cell damage) following the accidents to those lesions known to be produced by asphyxia support the asphyxia hypothesis. When patchy necrosis is found in the brain, it is like that which appears following oxygen shortage. Such areas of necrosis have not been observed as a result of toxic action of narcotics without anoxia. Degeneration of the lenticular nucleus is commonly produced by asphyxia but not directly by narcotics. Such degeneration is common in these cases. It seems safest to conclude that the cerebral damage is the result of asphyxia rather than of a direct action of the anesthetic agent.

It must be recognized that the mechanisms producing oxygen shortage may vary widely. Lack of cyanosis does not necessarily mean the absence of asphyxia of fatal degree (cf. anemia, or localized anoxia

as from localized ischemia, etc.). Asphyxia may be slowly and gradually accumulative, or it may be sudden through great obstruction of the airway, rapid cessation of respiration, or swift cardiac and circulatory impairment.

Abbott and Courville (1938) report a fatal case of severe degeneration of the globus pallidus following anesthesia. The authors conclude, on the basis of this case and the great majority of cases they have seen following carbon monoxide poisoning, that the globus pallidus of the lenticular nuclei is the region of the brain most sensitive to the effects of asphyxia. They believe the asphyxia which may have accompanied the anesthesia to be responsible.

It is unfortunate that this paper carries the implication in its title that nitrous oxide anesthesia was responsible for the accident, although on examination one learns that the patient received 6 grains of amytal (? by mouth), followed by nitrous oxide, ether, and ethylene. The paper contains the statement, "The damage to the brain was probably sustained during the period of cyanosis which began when ethylene was substituted for nitrous oxide." It had been stated earlier, that "cyanosis was thought to be due to spasm of the epiglottis." Granting that anoxia appears to be the likely cause of the disaster, certainly no evidence is presented that nitrous oxide ought to be incriminated over the other agents employed. While the reviewer has no wish to minimize the great hazard of anoxia during nitrous oxide anesthesia, the current tendency to attribute all neurologic accidents to asphyxia accompanying nitrous oxide anesthesia when this may be only one of several possible factors, is scarcely reasonable.

Fatal cerebral complications following nitrous oxide anesthesia in an obstetric patient are described by Brown, Collins, and Vaughan (1938). The oxygen percentage was, on occasion, allowed to get as low as 8.

Ford, Walsh, and Jarvis (1937) report the case of a young man who, following spinal, nitrous oxide and ether anesthesia with respiratory failure, presented grave brain damage. They suggest that anoxia alone may not be adequate to account for this damage, but that toxic action of the anesthetic agent plus asphyxia may be responsible. It seems unnecessary to postulate any cause other than anoxia in this case.

Much evidence is at hand to indicate that anoxia necessarily accompanies attempts to produce deep nitrous oxide anesthesia, if other depressant drugs have not been used. Bennett and Seevers (1937) have carried out experiments to find at what level anoxia contributes to the depressant action of nitrous oxide in normal men and whether or not anoxia produces a significant elevation of the sensory threshold for painful stimuli. They conclude that the oxygen intake must be reduced so low that the resulting anoxia is liable to contribute to postoperative morbidity (cf. Courville) before a significant increase in amnesia, analgesia, or anesthesia occurs. The responses of the normal

subjects to the use of 6 or 9 per cent oxygen were such as to suggest that the prolonged use of more than from 85 to 88 per cent nitrous oxide is unwise.

In considering anesthesia for intracranial surgery, Brennan (1938) describes the rise in cerebrospinal fluid pressure in man (four patients) under avertin anesthesia. This may be due to accompanying respiratory obstruction, perhaps to anoxia. Intracranial pressure seriously increases under ether, he finds. The use of a wide intratracheal tube is a great aid in reducing intracranial venous congestion. Cerebral venous congestion under nitrous oxide-oxygen anesthesia is usually due to inadequate oxygen, respiratory obstruction, or faulty position.

Complications of Spinal Anesthesia.—

Circulatory and Respiratory Depression During Spinal Anesthesia: The cause of the fall in blood pressure and the cause of respiratory depression during spinal anesthesia have been studied intensively recently. It has been considered that the primary fall in blood pressure during spinal anesthesia depends upon peripheral vasomotor paralysis.* Strong evidence supporting this has been obtained by studies which show the absence of this fall in pressure in sympathectomized dogs and cats. For further information see Bacq, Bouha, and Heymans (1934), Wilson, Roome, and Grimson (1936), and Bradshaw (1936). Of course, the total fall in pressure is due not only to this mechanism.

Several other mechanisms have been suggested as accounting for the fall in pressure beyond the level caused by peripheral vasodilatation. Nowak and Downing (1938) group these as follows:

1. Central anoxia secondary to the peripheral vasodilatation.
2. Central anoxia resulting from intercostal nerve paralysis and from paralysis of the phrenic nerve roots.
3. Medullary paralysis following direct extension of the anesthetic agent.
4. Central vasomotor and respiratory paralysis as a result of vascular absorption of the drug.

In an effort to appraise the relative importance of indirect central effects due to primary peripheral changes as opposed to direct central effects, they have undertaken a study of blood gases. They find in cats under spinal anethesia and light ether anesthesia that, whereas the arterial oxygen is little depressed, a considerable reduction occurs in the venous oxygen. They state that the increased arteriovenous oxygen difference is easily compensated for unless the phrenic or medullary centers are depressed or paralyzed. The validity of conclusions about spinal anesthesia drawn from this combination of ether and spinal anesthesia seems open to question. The well-known effects of ether upon the spleen and other blood reservoirs, its effect upon the heart muscle and respiration, etc., all seem to complicate the problem too much for definite conclusions to be reached.

*However, see the article by Smith, Rovenstine, and co-workers (1939).

Bonnycastle (1939) finds that the phrenic nerve roots in the spinal dural sac (of dogs) are paralyzed by concentrations of procaine which are less than those the respiratory center can withstand. He has found that the respiratory center can withstand concentrations of procaine somewhat greater than 1 per cent.

Shaw, Steele, and Lamb (1937) have studied the effect of spinal anesthesia upon the oxygen in the arterial and the venous blood (of dogs). They report an increase in the oxygen saturation of the arterial blood, a decrease in the oxygen content and saturation of the venous blood, and an increase in the arteriovenous oxygen difference; a stagnant type of anoxia was found to exist.

CoTui (1938) emphasizes the danger of using CO_2 as a respiratory stimulant when much of the sympathetic nervous system is paralyzed as it is in spinal anesthesia. Here CO_2 has a special "toxicity"; it lowers blood pressure by increasing peripheral capillary dilatation. However, Smith, Rovenstine, Goldring, Chasis, and Ranges (1939) report that "in human subjects with spinal anesthesia up to T3 or T2, and in whom all vasomotor reflexes other than those involving the head and arms are demonstrably blocked, neither CO_2 nor anoxemia has any depressor action" upon the circulation. This needs further checking.

CoTui points out that paralysis of the sympathetics checks adrenine secretion, and the loss of this may be responsible for some of the fall in blood pressure under spinal anesthesia.

Burstein (1939) recalls the work describing how a number of homeostatic mechanisms fail during high spinal anesthesia, in particular CoTui's emphasis upon the loss of compensating vasoconstriction when a considerable segment of the spinal cord has been paralyzed; Tournade and Schotte's demonstration of paralysis of the adrenalin-secretory mechanism; and paralysis of the sinoaortic mechanism as described by Heymans. Burstein calls attention to the fact that dogs are unable to compensate for postural blood pressure changes during spinal anesthesia as they can before and after. This is scarcely surprising, in the light of the above impairments.

Neurologic Damage Following Spinal Anesthesia: While persistent paralysis of nerve roots following spinal anesthesia is probably a rare event in well-established clinics, its occurrence is a serious complication of anesthesia. Ferguson and Watkins have investigated a series of cases in which paralysis (cauda equina syndrome) has followed the use of spinal anesthesia in man. They report that such damage is particularly liable to follow the use of duracaine. Duracaine heavy is said to have contained procaine HCl, planocaine brand, gliadin, and glycerin in a dilute solution (15 per cent) of ethyl alcohol. Later gum acacia was substituted for the gliadin. Since considerable uncertainty attached to which of the constituents was responsible for the toxic effects, Mac-

Donald and Watkins have investigated the matter experimentally and have produced with the agent a typical cauda equina syndrome (in cats): paralysis of the bladder, sphincter ani, and tail, sometimes weakness of the hind limbs, and also impairment of sensation.

Since the incidence in man is less than 1 per cent, for experimental purposes the dosage was stepped up to approximately five times that employed in man. Their experimental results (in cats) are shown in Table IX.

TABLE IX

AGENT	TOTAL NUMBER INJECTED	NOT PARALYZED	PARALYSIS OF BLADDER, ANAL SPHINCTER AND TAIL	PARALYSIS OF TAIL ONLY	TOTAL NUMBER PARALYZED	PERCENTAGE PARALYZED
Alcohol and glycerin	23	23	-	-	-	-
Heavy duracaine	23	10	9	4	13	56
Procaine 10 per cent (planocaine brand)	10	5	2	3	5	50
Procaine 10 per cent (novocaine brand)	23	17	4	2	6	26
Stovaine 5 per cent (Barker)	10	4	-	6	6	60

These results appear to demonstrate that the toxic agent is the procaine itself. The above figures do not, of course, establish any difference between brands of procaine. The failure to produce a single case of paralysis following alcohol and glycerin seems to rule them out as the toxic agent and also disposes of the idea that the condition results from needle trauma.

Table X (MacDonald and Watkins, 1938) is of interest.

TABLE X

RELATION OF PROCAINE-HCl DOSAGE TO INCIDENCE OF SYMPTOMS

PERCENTAGE CONCENTRATION	NUMBER OF ANIMALS	NUMBER SHOWING SOME PARALYSIS	PERCENTAGE PARALYSIS
2.5	20	0	0
5.0	20	2	10
10.0	56	24	43
20.0	8	4	80

This study, as the authors are aware, does not settle the matter of whether the addition of alcohol and glycerin enhances the toxic action of the procaine.

From this study it is plain that, in the concentrations ordinarily employed in man, commonly used spinal anesthetic agents are toxic to animals' nerve tissue to a serious degree. In man, however, their greater and more rapid dilution with cerebrospinal fluid prevents, except in rare cases, such paralysis. When such paralysis does occur,

it is usually of greatly limited extent. In the experimental animal the bony canal is more completely filled with nervous tissue, and a relatively smaller amount of cerebrospinal fluid is available for diluting purposes.

Lundy, Essex, and Kernohan (1933), following a prolonged temporary paralysis in man from the use of 10 per cent procaine, employ from 3 to 5 per cent solutions of procaine as they leave the syringe. There seems to be no excuse at this time for injecting greater than 5 per cent solutions of procaine into the subarachnoid space.

The work of MacDonald and Watkins emphasizes the value of a relatively slow spinal injection of anesthetic agents.

Ferguson and Watkins (1938) report fourteen cases of the cauda equina syndrome following spinal anesthesia. In thirteen of the cases heavy duracaine was used, and it probably was used in the remaining one. During this period some 1,700 spinal anesthesias were administered, most with duracaine.

References to damage from other agents used for spinal anesthesia are included.

Three of the cases came to autopsy. The sacral nerves showed fine vacuolation and were considered to show evidence of recent degeneration.

Kelman and Abbott (1938) have reviewed the literature on neural complications following spinocaine and other agents used in spinal anesthesia. They present five cases of prolonged neural damage following the use of spinocaine. Although the authors do not present desirable data regarding the total number of patients who received spinocaine, the fact that five cases of serious damage came under their observation is in itself a warning to caution in the use of the agent.

Koster, Kasman, and Shapiro (1937) attempted to produce in patients postspinal anesthesia headache, without success. A considerable bibliography is provided.

Foss and Bush (1939) present data on mortality and complications of spinal anesthesia.

"Rachiresistance": Sebrechts (1934), in considering the variations encountered in the clinic to a given spinal anesthesia technique, attributes some of the unexpected results to variation of individual susceptibility to the drugs employed. When unusually profound anesthesia follows the use of a normal dose of an agent, he terms the patient "rachisensible." When the anesthesia is insufficient or nonexistent, the patient is termed "rachiresistant." He believes this characteristic to be familial! He has found five members of one family to be "absolutely" resistant to spinal anesthesia (novocaine).

Black and Walters (1937) have reviewed the chief reasons for failure of spinal anesthesia:

I. Errors of technique.
   A. Inaccurate punctures.
   B. Faulty postural arrangement of the patient.
II. Inactive solutions.
III. Cord tumor, rarely.

They report two cases in which three uneventful injections in each patient (pantocain used most often) failed to produce more than an extremely small effect. The above three chief sources of error seemed to be ruled out.

The phenomenon of sensitivity to the agents used in spinal anesthesia is well established. Perhaps true resistance also exists and should be classified as an idiosyncrasy. However, when the reviewer's "spinals" fail, he prefers to attribute the failure to shortcomings of his own technique.

Thompson (1934) reports a case in which spinal anesthesia for operation on a large tumor of the cauda equina was attempted. The injection of 100 mg. of procaine into the lumbar subarachnoid region, above the tumor, produced a girdle of anesthesia above the level of the tumor, yet complete sensation was retained in the operative field. These observations are of particular importance because they support the assumption that drugs used in spinal anesthesia produce their effect by a blockade of impulses in the spinal root filaments rather than by a direct action on sensory fibers in the cord itself.

Sensitivity or Idiosyncrasy to Anesthetic Agents.—

Gömöri (1936), in reviewing many accidents under local anesthesia, divides the accidents into two rather distinct groups. In the first group he places the cases which present a true intoxication resulting from overdosage. Here typical symptoms and signs are: psychic excitation, mental confusion, transient palsies, violent clonic convulsions. Fatalities are uncommon in this group. The second group is composed of those cases which show hypersensitivity to the drug used. Analysis of cases falling into the second group demonstrates that the quantity of the anesthetic used in the great majority of cases was extremely small; the concentration employed was well within safe limits; safe quantities of epinephrine were used. Outstanding symptoms and signs are anxiety, dizziness, paleness with or without cyanosis, a clammy, cold skin, extremely feeble pulse, and often loss of consciousness; often muscular twitchings, even convulsions, are observed. Death frequently occurs within a few minutes of the onset of symptoms.

Goodman (1939) discusses cutaneous hypersensitivity to the procaine anesthetics and correlates hypersensitivity with chemical structure. He also makes the interesting observation that persons whose skins manifest the very highest degree of contact-type allergic eczematous sensitivity do not necessarily exhibit sensitivity of their mucous membranes.

Hailey and Hailey (1937) report three cases of severe dermatitis following the use of nupercaine ointment.

Theodore (1938) reports a case of sensitiveness to larocain.

Kotz, Roth, and Ryon (1938) report the death of a patient (toxemia of pregnancy, toxic myocarditis) following 31 c.c. paraldehyde by rectum. They review the literature on paraldehyde.

See also the section on neurologic complications of spinal anesthesia.

Explosions during Anesthesia.—

Compared with other surgical risks, the risk of explosion of the anesthetic agent is statistically small. There are many intangible factors, however, which increase the importance of this above its numerical value. As with many newsworthy events, an explosion and the circumstances surrounding it may be greatly exaggerated, leading to bad relationships between the public and hospitals when such accidents occur. This is aside from the shock to all those intimately concerned. Woodbridge (1939) has considered the hazard of explosion from the point of view of the anesthetist. Answers to a questionnaire sent out by Woodbridge concerning explosion rate are as follows:

AGENT	ADMINISTRATION	EXPLOSION RATE/100,000
Ether	1,975,342	1.72 ± 0.31
Ethylene	326,798	2.44 ± 0.86
Cyclopropane	259,985	3.85 ± 1.22

The standard deviations are so large that it is impossible to draw any conclusions as to difference from these data, as he is aware.

Woodbridge's data do not reveal whether the explosions were occasioned by the use of the cautery, the careless use of light, fires, electrical equipment, or by other easily preventable means, or by the dread static discharge. This, it seems to this reviewer, is one of the basic questions to be answered. If a surgeon decides that the use of the cautery in a questionable case is so important that he considers the risk of explosion justified and if a fatal explosion occurs, that is one thing. If, on the other hand, all precautions known have been taken and a static discharge sets off a fatal explosion, that is quite a different story. A very important question is: How often has static electricity caused an explosion of serious consequence and how often fatalities with the common anesthetic agents? While Woodbridge's data do not answer this question, the answer will perhaps emerge from the valuable data being collected by the American Society of Anesthetists.

The nearly universal opinion that ether, ethylene, or cyclopropane presents an equal explosion hazard must be challenged. It is probable that such a general belief grew out of the fact that each agent in its anesthesia range can develop an explosive force of fatal violence. Other factors must be considered, such as the violence of explosion, etc. The series of fatal explosions (static) under cyclopropane which have oc-

curred recently is a strong indication that the explosion hazard from static electricity is greater with cyclopropane than it is with ether.

Horton (1939) has considered the factors which affect the occurrence and prevention of electrostatic sparks during anesthesia. He finds that a high relative humidity is not adequate to prevent the building up of large charges in an operating room. In itself it is an inadequate safeguard. He recommends that any electrical interconnection in close proximity to the breathing tubes, the mask, or other portion of the rebreathing system be discontinued. Cushioned stools should never be used in the operating room. Woolen blankets and wool or silk outer garments should be prohibited.

When closed anesthesia systems are used, it is probable that no explosive mixture will exist beyond the radius of a foot surrounding a leak. This, of course, does not apply if the anesthetic mixtures are deliberately discharged into the room.

Horton discusses the dangers of grounding patients. These arise in the danger of an electrical shock coming from the electrical equipment in use, as well as from the increased hazard of an electrostatic spark between the grounded system and a nongrounded person who, through error, might approach the system. He also points out the hazards of low resistance intercoupling of patient, operating table, gas machine, and anesthetist. He recommends the use of high resistance intercoupling. Such intercoupling requires conscious effort. If imperfectly arranged, it may lead to a dangerous sense of security.

An alternative to Horton's system might be for the anesthetist to maintain constant contact with the patient (away from the airways) and frequent contact with the other bodies (operating table, gas machine). If the contact must be broken, when the anesthetist resumes it, the patient should always be approached by making contact as far from the airways and any potential leaks as possible, always at least one foot from possible leaks. The reviewer is in no position to argue the merits of this system over that proposed by Professor Horton. It has some support in its considerable use. In any case, the anesthetist must take the responsibility for keeping all bystanders and members of the operating team at least one foot away from potential leaks.

Horton points out the hazards incident to the disconnecting of airways, breathing bag, etc., during operation.

Connell (1939) has considered the hazard of explosion from the point of view of the manufacturer of gas machines.

Five classes of ignition may produce explosions of combustive anesthetic mixtures:

1. Intermixing of combustible gases under high pressure.
2. Sparks due to mechanical friction.
3. Catalytic action. (This is of doubtful importance. Possible catalysts that need study are soda lime, dry metal oxides, the platinum

of mouth dentures; possible impurities in the agents used might be added.)

4. Ignition by open flame, sparking electrical apparatus and cautery, diathermy, high frequency apparatus, and x-ray apparatus. (These latter should never be used in the presence of inflammable anesthetic agents.)

5. Electrostatic spark. No degree of room humidity, however high, totally prevents the development of momentary static charges.

Safeguards from static electricity are:

1. Wet breathing circuit at start.

2. Condensation of patient's breath.

3. Use of an electrolyte solution (calcium chloride) to keep the rubber of the breathing tubes conductive. (Wipe new rubber over with 4 per cent calcium chloride and rinse the rubber each time it is washed with rinse water containing a few tablespoonfuls of this solution. This will tarnish metal.)

4. Intercoupling with high resistance safeguard.

5. Room humidification.

Anesthetic apparatus.

1. The apparatus should be constructed so that intermixture of gases at high pressure is impossible.

2. It should be constructed of sparkless metals.

3. It should be tight and with central spill valve.

4. The apparatus should not be subjected to open flame or electrical apparatus.

5. The apparatus should be emptied and washed free of combustive material when not in use.

6. Conduit connections, metal to metal, should not be disturbed or reconnected during use.

7. The apparatus should not be covered while idle.

8. Dry, hot blankets should not be carried past it when in use.

9. It should be intercoupled electrically with patient and anesthetist before anesthesia is started and this intercoupling maintained until after washed out.

10. Intercoupling should be remote from gas spillage and of the high resistance type.

11. Rubber parts should be treated with electrolyte and kept moist inside during use.

Eversole, Sise, and Woodbridge (1937) state that high frequency electrical apparatus should not be used in operating rooms in which cyclopropane is being used, because of the danger of sparking from scattered points in the vicinity of such apparatus. This includes x-ray apparatus as well as electrosurgical units for cutting and coagulation. They do not consider that the low voltage actual cautery presents this same sparking danger, although, of course, the glowing cautery itself could initiate an explosion.

Among the usual hazards and precautions, Hasler (1938) points out the dangers from laryngoscope and bronchoscope if faulty insulation leads to spark (loose bulb, etc.). He also points out dangers of dry air effected by some air-conditioning apparatuses.

The (British) Medical Research Council is investigating the question of explosions from static sparks, with the assistance of the National Physical Laboratory. Their conclusions are to be published soon, it is stated.

The following writers have also considered the explosion hazard during anesthesia, but not so thoroughly as have Woodbridge, Horton, and Connell: Phillips (1936), Toland and Kroger (1937), Becker (1937), Thalheimer (1938), Kaye (1938), and Becker and Woltersdorf (1938).

Impurities in Ether.—

To what extent the complications of anesthesia are related to impurities in the ether used is not clear. We have little information as to how such impurities affect the conduct of anesthesia. A finding of Knoefel and Murrell in mice (1935) concerns the rate of production of anesthesia by ether containing aldehyde and peroxide. They report that, when small amounts of these agents are present in the ether, a significant slowing of the rate of induction occurs (measured by loss of posture). A likely explanation offered for this effect of the impurities is that they act by slowing the rate of entrance of ether into the blood stream.

They also report that 0.2 per cent aldehyde and 0.07 per cent peroxide do not significantly alter the acute toxicity of the "ether."

Ether From Large or Small Containers?—

The question of whether ether supplied in 27- or 55-pound drums is as satisfactory for anesthesia as that provided in from one-quarter- to one-pound cans is a matter of considerable economic importance. Hediger and Gold (1935) attempt to show that ether supplied in large containers is as satisfactory as that in the small ones, even though the ether from the large containers had been exposed to the air for as long as sixty-eight days.

This matter can hardly be considered settled as yet, for there is some evidence that one lot of ether will decompose faster than another one. To rule out this hazard, the study would have to consider many more drums than was the case here. Doubtless, frequent and thorough cleaning of the small containers filled from larger ones could eliminate the possibility of decomposition products gradually appearing in them, but such would always be a possibility unless this was taken carefully into consideration. The fire and explosion hazard of the nearly empty but vapor-filled large drums, as well as the general fire hazard of a large bulk of ether, cannot be disregarded. The problem is an involved one; it needs further study.

(To be continued. The references will accompany the last part.)

Review of Recent Meetings

THE SOCIETY OF UNIVERSITY SURGEONS

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THE second annual meeting of the Society of University Surgeons was held Feb. 9 and 10, 1940, in New York City at the New York Hospital. Most of the papers presented at this meeting are to be found in this issue of SURGERY. Brief abstracts of other papers presented at that meeting are summarized herewith.

William J. German and **Max Teffel**, Yale University, **Surgical Production of Collateral Intracranial Circulation. An Experimental Study.**—The authors described a method of temporal and suboccipital muscle grafts to the surface of the brain in order to produce an accessory arterial blood supply. The animals employed were monkeys with experimentally ligated carotid and vertebral arteries in various combinations.

D. Henry Poer, Emory University, Atlanta, Ga., **Clinical Experience With the Use of Di-Hydro-Tachysterol (AT-10-), in the Treatment of Ten Cases of Hypoparathyroidism.**—The author in a series of ten cases of parathyroid tetany following thyroidectomy employed di-hydro-tachysterol and vitamin D_2. These were thought to be equally effective in controlling the symptoms and maintaining serum calcium levels near normal. Each preparation has advantages over parathyroid hormone if its use is continued over a long period of time.

Cobb Pilcher, Vanderbilt University, **Experimental Cerebral Trauma. II. Further Observations on the Fluid Content of the Brain Following Trauma to the Head.**—Experiments by the author were presented and interpreted to show a marked stability of the fluid content of the brain tissue even after trauma. The author furthermore was of the opinion that his experiments suggested that cerebral edema would not occur in animals following trauma.

Thomas E. Wyatt and **Cobb Pilcher**, Vanderbilt University, **Experimental Cerebral Trauma. III. The Effects of Acute Uremia, of Venous Obstruction, of Hyperthermia, and of Intensive Irradiation on the Fluid Content of the Dog's Brain.**—These authors studied the fluid content of various portions of the brains in dogs after bilateral nephrectomy, bilateral ureteral ligation, venous obstruction, severe hyperthermia and intensive irradiation. The percentage of fluid was slightly but consistently elevated in cerebral and cerebellar gray matter and in the brain stem after hyperthermia. The fluid contents of the brains in all other experiments were within normal limits.

Alexander Brunschwig, University of Chicago, **The Localization of Evans Blue in Malignant Tumors.**—The author reported selective localization of Evans blue in twenty of thirty patients with various types of malignant neoplasms following intravenous injections of 50 to 100 mg. of the dye.

Book Reviews

A Bibliography of the Writings of Harvey Cushing. By The Harvey Cushing Society. Cloth. Pp. 108, with frontispiece. Springfield, Ill. Charles C. Thomas, Publisher, 1939. $5.

On the occasion of his seventieth birthday, the Harvey Cushing Neurological Society presented the late Harvey Cushing with a small tome containing a complete list of his papers and books by title, his vita, and a list of papers published by his associates from his clinics at Baltimore and Boston. Appended also are the names of those who successively were his assistants in neurological surgery and appointees in the surgical research laboratories at Baltimore and Boston.

During a busy life, Harvey Cushing wrote 13 monographs and more than 300 papers. An additional 327 papers written by his associates under his direction are listed too.

An annotation, acquainting the reader with the circumstances under which the books and papers were written and the occasion of their presentation, accompanies the title of each book and a large number of the papers. It is extraordinarily interesting to peruse these titles and to appreciate that they were the work of one man. *The Pituitary Body* (1912), *Life of Sir William Osler* (1925), *Consecratio Medici* (1928), *Intracranial Tumours* (1932), and *Meningiomas* (1938) are monographs, each of which represents the best effort of its kind. His papers on typhoidal cholecystitis and cholelithiasis (1898) and the experimental formation of gall stones (1899), the bacteriology of the upper portion of the alimentary canal written with L. E. Livingood, experimental studies on brain compression done in Kronecker's laboratory in Bern (1902), routine determination of arterial tension in operating room and clinic (1903), and his methods of accomplishing decompression in inoperable brain tumor (1905) are some of his early papers which foreshadowed his genius.

The number of persons among his assistants who have established themselves as leaders in their fields gives further evidence of the great genius of Harvey Cushing. He attracted the best talent and left an indelible stamp on all of them.

This monograph outlines the versatile and remarkable accomplishment of one man during a long life of unceasing labor. It is a most animating and exceptional record. The book can be recommended, not alone as a key to Harvey Cushing's papers, but also because it details the literary contributions of a singularly stimulating and useful life.

Harvey Cushing's Seventieth Birthday Party, April 8, 1939: Speeches, Letters and Tributes. Cloth. Pp. 146, with 9 illustrations. Springfield, 1939, Charles C. Thomas, Publisher. $3.

The Harvey Cushing Society, during their eighth annual meeting held at New Haven, Conn., celebrated Harvey Cushing's seventieth birthday, April 8, 1939. The occasion was signalized by a dinner at which were read telegrams and greetings from admiring friends, pupils and former patients from all over the world. Arnold C. Klebs, of Switzerland, life-long friend of Cushing, returned for the occasion.

Dr. Cushing responded in a light vein to the numerous toasts and felicitations but concluded on a serious note, exhorting neurosurgeons to serious thought as well as action. Said Dr. Cushing: "Neurology, broadly speaking, is a field for thinkers as well as doers, and it is gratifying that the surgical doers for almost the first time in the history of medicine have come to be recognized as deserving of memberships in the societies of those otherwise engaged. This being so, we must look to it that we justify this recognition by the character of our work."

An appreciation of "Harvey Cushing at Seventy," written by Henry R. Viets and reprinted from the *New England Medical Journal*, contains a commendable appraisal of Cushing's surgical and literary activities. A reprint of a similar article by John F. Fulton, under the title of "Harvey Cushing and Roentgenology," relates Cushing's great interest in the technique of taking x-ray films during the early days at the Johns Hopkins University. The concluding paper of the monograph, entitled "Notes on the Formative Period of a Neurological Surgeon," written also by Henry R. Viets, relates some very interesting episodes from Cushing's life: of his interest in anesthesia, his unrivalled capacity as a note-taker on clinical cases, manifested as early as his internship at the Massachusetts General Hospital, the notes being adorned by artistic sketches, and finally of Cushing's role in initiating in this country clinical studies in blood pressure.

These fragmentary accounts of a versatile and great man will some day be recounted in appropriate biographies, for a life so distinguished has many lessons to teach.

Fetal and Neonatal Death. A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life. By Edith L. Potter, M.D., and Fred L. Adair, M.D. Cloth. Pp. 207, with 31 illustrations. Chicago, 1940, University of Chicago Press. $1.50.

This unique book brings together and correlates statistical, clinical, anatomic, and pathologic data on fetal and neonatal deaths in such a manner that one interested in any of its phases can quickly find a ready answer to his query. For the specialist caring to go into greater detail, an adequate bibliography is furnished at the end of each chapter. Heretofore, this information has not been readily accessible in any single text and the interested student or graduate would have been forced to consult innumerable articles and texts.

The book begins with statistical expressions which are in general use today and these figures prove, though the authors have not emphasized this specifically, that current methods of examination and reporting stillbirths and neonatal deaths are grossly deficient. For instance, a report of the stillbirths in the registration area of the United States indicates that 78 per cent of those delivered under four months are males. This gives a sex ratio of 355 males to every 100 females, a figure which is more than twice as great as the highest scientific estimate for the conception ratio and more than three times as great as the usually quoted sex ratio of term and near-term fetuses. This emphasizes the difficulty in determining the sex of the early fetus by casual observation of the external genitals and re-emphasizes the importance of careful external and internal examination by someone especially versed in such detection. Furthermore, the fact that only 26 per cent of 125 infants were proved by autopsy to have died of prematurity, whereas 57 per cent of a comparable series of 166 infants without autopsy were said to have succumbed from prematurity, indicates that the causes of death in this group of patients are not being accurately determined

and that stillbirths and death certificates on them are not correctly reported, probably largely as a result of insufficient data and inadequate examination.

The way is pointed to the most precise method of determination of the causes of natal and neonatal deaths and only with a regime such as the one employed by the authors will the cause of death in individual or large series of fetuses and infants be correctly determined. The difficulty encountered in comparing reported series shows the need of greater uniformity in terminology of just what constitutes abortion, prematurity, stillbirths, etc., and shows the difficulties arising in the absence of a uniform classification of causes of fetal and neonatal death.

The embryologic and anatomic descriptions of fetuses and their individual organs are not extensive, but yet they are adequate for a thorough understanding of the general and special pathologic problems that are encountered in death of these individuals. The pathologic findings and possibilities are described in detail.

The 1939 Yearbook of General Surgery. Edited by Evarts A. Graham, M.D. Cloth. Pp. 796, with 304 illustrations. Chicago, 1939, The Yearbook Publishers. $3.

Perusal of this volume will give the reader a bird's-eye view of some of the more important contributions to the literature of surgery during the latter months of 1938 and the early months of 1939. One of the most valuable parts of the volume are the many editorial comments of the editor. He who becomes familiar with the *Yearbook of General Surgery*, by study, year after year, cannot help but absorb something of the conservative philosophy of the well-known editor. Where else can one find the reactions of one surgeon who speaks with authority on so many surgical problems. That the editor know his yearbook is apparent when one notes how often he refers to previous reviews in earlier years.

New and important papers on anesthesia, asepsis, and surgical technique are reviewed. The materials in the section on the biliary tract are particularly good. In this section and in the chapters on thoracic surgery, the reader is especially glad to have the editor's comments.

In an appropriate foreword Dr. Graham refers to those developments in surgery during the year which are worthy of particular notice. This book can be recommended enthusiastically to all general surgeons as affording a synopsis of some of the more important and practical surgical papers of the year that has passed.

Les "pièges" de la chirurgie en diagnostic et thérapeutique: Erreurs et fautes ou faits présumés tels conditions et limites de la responsabilité. By Prof. E. Forgue, membre de l'Académie de chirurgie, and Prof. Aimes, Professeur agrégé à la Faculté de Montpellier. Cloth. Pp. 509. Paris, 1939, Masson et Cie. 120 francs.

The intriguing title of this book, "Snares in Surgery," was selected by the authors in preference to "Errors and Faults in Surgery" because the latter might create the wrong impression. Fully cognizant of somewhat similar previous expositions, such as the German edition of Stitch and Makkas, they have attempted, in a different manner, to present a collection of facts representing misfortunate occurrences more often than surgical errors and to define the legal responsibilities of the surgeon.

WILLIAM J. MAYO
1861-1939

CHARLES H. MAYO
1865-1939